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In re Patent Application of:
Nikolay Khanzhin et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

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For: SUBSTITUTED P-DIAMINOBENZENE DERIVATIVES | Examiner: Not Yet Assigned

AFFIRMATION OF PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
Denmark	PA200300441	March 21, 2003

A certified copy of the aforesaid Danish and U.S. Applications were received by the International Bureau on April 1, 2004 during the pendency of International Application No. PCT/DK2004/000186. A copy of Form PCT/IB/304 is enclosed.

Dated: September 20, 2005

Respectfully submitted,

By _____
S. Peter Ludwig
Registration No.: 25,351
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

PCT/DK 2004/000186

Kongeriget Danmark

Patent application No.: PA 2003 00441

Date of filing: 21 March 2003

Applicant: (Name and address)
H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

Title: Substituted p-diaminobenzene derivatives.

IPC: -

This is to certify that the attached documents are exact copies of the above-mentioned patent application as originally filed.

PRIORITY DOCUMENT
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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

04 February 2004

Ella Vang M. Hansen

PATENT- OG VAREMÆRKESTYRELSEN

Substituted p-diaminobenzene derivatives

Field of the invention

The present invention relates to novel substituted aniline derivatives being openers of the KCNQ family potassium ion channels. The compounds are useful for the prevention, treatment and inhibition of disorders and diseases being responsive to opening of the KCNQ family potassium ion channels, one such disease is epilepsy.

Background of the invention

Ion channels are cellular proteins that regulate the flow of ions, including potassium, calcium, chloride and sodium into and out of cells. Such channels are present in all animal and human cells and affect a variety of processes including neuronal transmission, muscle contraction, and cellular secretion.

Humans have over 70 potassium channel subtypes (Jentsch *Nature Reviews Neuroscience* **2000**, 1, 21-30) with a great diversity with regard to both stucture and function. Neuronal potassium channels, which are found in the brain, are primarily responsible for maintaining a negative resting membrane potential, as well as controlling membrane repolarisation following an action potential.

One subset of potassium channel genes is the KCNQ family. Mutations in four out of five KCNQ genes have been shown to underlie diseases including cardiac arythmias, deafness and epilepsy (Jentsch *Nature Reviews Neuroscience* **2000**, 1, 21-30).

The KCNQ4 gene is thought to encode a potassium channel found in outer hair cells of the cochlea, mutations in this gene can lead to a form of inherited deafness. KCNQ1 (KvLTQ1) is co-assembled with the product of the KCNE1 (minimal K(+)-channel protein) gene in the heart to form a cardiac-delayed rectifier-like K(+) current. Mutations in this channel can cause one form of inherited long QT syndrome (LQT1), as well as being associated with a form of deafness (Robbins *Pharmacol Ther* **2001**, 90, 1-19).

The genes KCNQ2 and KCNQ3 were discovered in 1988 and appear to be mutated in a rare inherited form of benign familial neonatal convulsions (Rogawski *Trends in*

Neurosciences **2000**, 23, 393-398). The proteins encoded by the KCNQ2 and KCNQ3 genes are localised in the pyramidal neurons of the human cortex and hippocampus, regions of the brain associated with seizure generation and propagation (Cooper et al. *Proceedings National Academy of Science U S A* **2000**, 97, 4914-4919).

KCNQ2 and KCNQ3 are two potassium channel subunits that form "M-currents" when expressed in vitro. The M-current is a non-inactivating potassium current found in many neuronal cell types. In each cell type, it is dominant in controlling membrane excitability by being the only sustained current in the range of action potential initiation (Marrion *Annual Review Physiology* **1997**, 59, 483-504). Modulation of the M-current has dramatic effects on neuronal excitability, for example activation of the current will reduce neuronal excitability. Thus openers of these channels, or activators of the M-current, may be of use in the treatment of disorders of neuronal hyperexcitability including convulsive disorders, epilepsy and neuropathic pain.

Retigabine (D-23129; N-(2-amino-4-(4-fluorobenzylamino)-phenyl) carbamic acid ethyl ester) and analogues thereof are disclosed in EP554543. Retigabine is an antiepileptic compound with a broad spectrum of action and potent anticonvulsant properties, both in vitro and in vivo. It is active after oral and intraperitoneal administration in rats and mice in a range of anticonvulsant tests including: electrically induced seizures, seizures induced chemically by pentylenetetrazole, picrotoxin and N-methyl-D-aspartate (NMDA) and in a genetic animal model, the DBA/2 mouse (Rostock et al. *Epilepsy Research* **1996**, 23, 211-223). In addition, retigabine is active in the amygdala kindling model of complex partial seizures, further indicating that this compound has potential for antiepileptic therapy. In clinical trials, retigabine has recently shown effectiveness in reducing the incidence of seizures in epileptic patients (Bialer et al. *Epilepsy Research* **2002**, 51, 31-71).

Retigabine has been shown to activate a K(+) current in neuronal cells and the pharmacology of this induced current displays concordance with the published pharmacology of the M-channel, which recently was correlated to the KCNQ2/3 K(+) channel heteromultimere. This suggests that activation of KCNQ2/3 channels may be responsible for some of the anticonvulsant activity of this agent (Wickenden et al.

Molecular Pharmacology **2000**, 58, 591-600) – and that other agents working by the same mechanism may have similar uses.

KCNQ channels have also been reported to be upregulated in models of neuropathic pain (Wickenden et al. *Society for Neuroscience Abstracts* **2002**, 454.7), and potassium channel modulators have been hypothesised to be active in both neuropathic pain and epilepsy (Schroder et al. *Neuropharmacology* **2001**, 40, 888-898).

Retigabine has also been shown to be beneficial in animal models of neuropathic pain (Blackburn-Munro and Jensen *European Journal of Pharmacology* **2003**, 460, 109-116), thus we suggest that openers of KCNQ channels will be of use in treating pain disorders including neuropathic pain.

Finally, retigabine and KCNQ modulators may exhibit protection against the neurodegenerative aspects of epilepsy, as retigabine has been shown to prevent limbic neurodegeneration and the expression of markers of apoptosis following kainic acid-induced status epilepticus in the rat (Ebert et al. *Epilepsia* **2002**, 43 Suppl 5, 86-95). This may have relevance for preventing the progression of epilepsy in patients, i.e. be anti-epileptogenic. Retigabine has also been shown to delay the progression of hippocampal kindling in the rat, a further model of epilepsy development (Tober et al. *European Journal Of Pharmacology* **1996**, 303, 163-169).

Thus we suggest that these properties of retigabine and KCNQ modulators may prevent neuronal damage induced by excessive neuronal activation, and may be of use in the treatment of neurodegenerative diseases, and be disease modifying (or antiepileptogenic) in patients with epilepsy.

WO01/022953 describes the use of retigabine for prophylaxis and treatment of neuropathic pain such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neuropathic pain related to migraine.

WO02/049628 describes the use of retigabine for the prevention, treatment, inhibition and amelioration of anxiety-related conditions such as anxiety, generalized anxiety

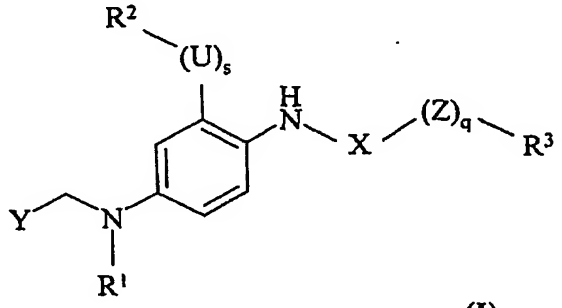
disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias.

WO97/15300 describes the use of retigabine for the treatment of neurodegenerative disorders such as alzheimer's disease; huntington's chorea; multiple sclerosis; amyotrophic lateral sclerosis; Creutzfeld-Jakob disease; Parkinson's disease; encephalopathies induced by AIDS or infection by rubella viruses, herpes viruses, borrelia and unknown pathogens; trauma-induced neurodegenerations; neuronal hyperexcitation states such as in medicament withdrawal or intoxication; and neurodegenerative diseases of the peripheral nervous system such as polyneuropathies and polyneuritides.

Summary of the invention

One object of the present invention is to provide novel compounds, which are potent openers of the KCNQ family potassium channels.

Accordingly, the present invention relates to substituted p-diaminobenzene derivatives of the general formula I



(I)

wherein

s is 0 or 1;

U is O, S, SO_2, SO_2NR^{11}, CO-O or CO-NR^{11}; wherein R^{11} is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_1-

$_{6}$-alk(en/yn)yl; or $\mathbf{R^2}$ and $\mathbf{R^{11}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

q is 0 or 1;

X is CO or SO_2; with the proviso that **q** is 0 when **X** is SO_2;

Z is O or S;

$\mathbf{R^1}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

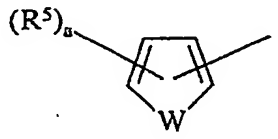
$\mathbf{R^2}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl and $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; wherein $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;
provided that when $\mathbf{R^2}$ is halogen or cyano then s is 0; and

provided that U is O or S when s is 1 and R^2 is a hydrogen atom or acyl;

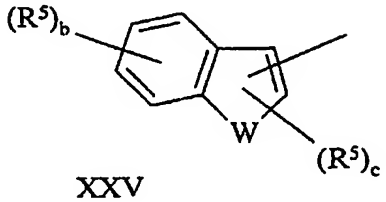
R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, heterocycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, -$NR^{12}R^{12'}$; wherein R^{12} and $R^{12'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or R^{12} and $R^{12'}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

and

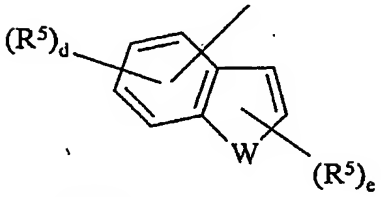
Y represents a group of formula XXIV, XXV, XXVI, XXVII or XXVIII:



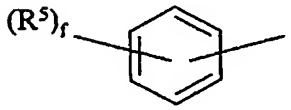
XXIV



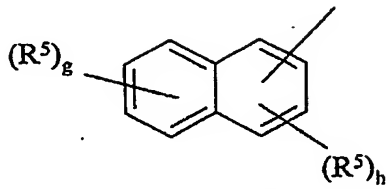
XXV



XXVI



XXVII



XXVIII

wherein

the line represents a bond attaching the group represented by Y to the carbon atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yloxy, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -$NR^7R^{7'}$, -S-R^8 and -SO_2R^8, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring which optionally contains one or two heteroatoms;

$\mathbf{R^6}$ and $\mathbf{R^{6'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

$\mathbf{R^7}$ and $\mathbf{R^{7'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

$\mathbf{R^8}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein $\mathbf{R^9}$ and $\mathbf{R^{9'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

or salts thereof.

Detailed description

In one embodiment, the invention relates to compounds of formula I, wherein s is 1.

In another embodiment, the invention relates to compounds of formula I, wherein s is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is O.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is S.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is SO_2.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is SO_2NR^{11}.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is CO-O.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is CO-NR^{11}.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^{11}}$ is a hydrogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 1.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 1 and **Z** is O.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 1 and **Z** is S.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1 and **Z** is O.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1 and **Z** is S.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO and **q** is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2 and **q** is 0.

In another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^1}$ is selected from the group consisting of acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

One embodiment of the invention relates to compounds of the general formula I, wherein $\mathbf{R^1}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

A preferred embodiment of the invention relates to compounds of the general formula I, wherein $\mathbf{R^1}$ is selected from the group consisting of hydrogen and C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^1}$ is C_{1-6}-alk(en/yn)yl, typically C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^1}$ is a hydrogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is selected from the group consisting of hydrogen, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl and $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; wherein $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms; provided that **U** is O or S when s is 1 and $\mathbf{R^2}$ is a hydrogen atom or acyl;.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and cyano; provided that when $\mathbf{R^2}$ is halogen or cyano then s is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl and cyano;
provided that when $\mathbf{R^2}$ is halogen or cyano then s is 0.

In a preferred embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl, halogen and cyano;
provided that when $\mathbf{R^2}$ is halogen or cyano then s is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is C_{1-6}-alk(en/yn)yl, C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is C_{3-8}-cycloalk(en)yl, typically C_{3-6}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is Ar-C_{1-6}-alk(en/yn)yl, typically Ar-C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is a halogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is halo-C_{1-6}-alk(en/yn)yl, typically halo-C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ is cyano.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, U is O and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-

cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl and halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is O and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is O and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is S and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl and Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is S and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl and Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and cyano.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl and cyano.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, halogen and cyano.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is CO-O and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is CO-O and $\mathbf{R^2}$ is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is CO-NR^{11}, $\mathbf{R^{11}}$ is a hydrogen atom and $\mathbf{R^2}$ is different from C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl and Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is CO-NR^{11} and $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is CO- NR^{11} and $\mathbf{R^2}$ is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^{11}}$ is a hydrogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is selected from the group consisting of heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, acyl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-

cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, -$NR^{12}R^{12'}$; wherein $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar and halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yl-Ar.

In a preferred embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl, typically C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is Ar-oxy-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is halo-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^3}$ is halo-C_{1-6}-alk(en/yn)yl-Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1, **Z** is O and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-

alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1, **Z** is O and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1, **Z** is O and $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl, typically C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1, **Z** is S and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 1, **Z** is S and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl and Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 0, $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-

alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar and halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 0, $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yl-Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2, **q** is 0 and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2, **q** is 0 and $\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl and Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yloxy, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy, halogen, $-NR^7R^{7'}$, $-S-R^8$ and $-SO_2R^8$, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, Ar, C_{1-6}-alk(en/yn)yloxy, halogen, $-NR^7R^{7'}$, $-S-R^8$ and $-SO_2R^8$, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

In a preferred embodiment, the invention relates to compounds of formula I, wherein each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, Ar, C_{1-6}-alk(en/yn)yloxy, halogen, -S-R^8 and -SO_2R^8, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is C_{1-6}-alk(en/yn)yloxy.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is a halogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is -S-R^8.

In yet another embodiment, the invention relates to compounds of formula I, wherein one $\mathbf{R^5}$ is -SO_2R^8.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

In a preferred embodiment, the invention relates to compounds of formula I, wherein two adjacent $\mathbf{R^5}$ together form
$-(CH_2)_{n'}-CH_2-$, $-CH=CH-(CH_2)_{m'}-$, $-CH_2-CH=CH-(CH_2)_{p'}-$, $-CH=CH-CH=CH-$,
$-(CH_2)_{n'}-O-$, $-O-(CH_2)_{m'}-O-$, $-CH_2-O-(CH_2)_{p'}-O-$, $-CH_2-O-CH_2-O-CH_2-$,
$-(CH_2)_{n'}-S-$, $-S-(CH_2)_{m'}-S-$, $-CH_2-S-(CH_2)_{p'}-S-$, $-CH_2-S-CH_2-S-CH_2-$,

$-(CH_2)_{n'}-NH-$, $-NH-(CH_2)_{m'}-NH-$, $-CH_2-NH-(CH_2)_{p'}-NH-$, $-CH=CH-NH-$, $-O-(CH_2)_m-NH-$, $-CH_2-O-(CH_2)_{p'}-NH-$ or $-O-(CH_2)_{p'}-NH-CH_2-$, $-S-(CH_2)_{m'}-NH-$, $-N=CH-NH-$, $-N=CH-O-$ or $-N=CH-S-$, wherein m' is 1, 2 or 3, n' is 2, 3 or 4 and p' is 1 or 2.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent $\mathbf{R^5}$ together form $-CH_2-O-CH_2-$.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent $\mathbf{R^5}$ together form $-CH=CH-CH=CH-$.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^7}$ and $\mathbf{R^{7'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^7}$ and $\mathbf{R^{7'}}$ are independently selected from the group consisting of hydrogen and C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein both $\mathbf{R^7}$ and $\mathbf{R^{7'}}$ are C_{1-6}-alk(en/yn)yl, typically C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^8}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar .

In a preferred embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^8}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl and Ar .

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2, **q** is 0 and $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl, with the proviso that $\mathbf{R^3}$ is different from a methyl group.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 0, $\mathbf{R^3}$ is a methyl group and **X** is different from SO_2.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2, **s** is 1 and **U** is different from O.

In yet another embodiment, the invention relates to compounds of formula I, wherein **s** is 1, **U** is O and **X** is different from SO_2.

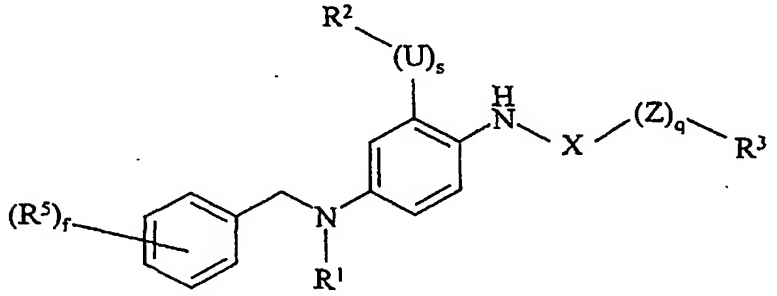
In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 0 and $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl, with the proviso that $\mathbf{R^3}$ is different from a methyl group.

In yet another embodiment, the invention relates to compounds of formula I, wherein **s** is 1, **U** is different from O, **X** is CO, **q** is 0 and $\mathbf{R^3}$ is a methyl group.

In yet another embodiment, the invention relates to compounds of formula I, wherein **s** is 1, **U** is O, **X** is CO, **q** is 0 and $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl, with the proviso that $\mathbf{R^3}$ is different from a methyl group.

The molecular weight of the compounds of the invention may vary from compound to compound.The molecular weight of a compound of formula I is typically more than 200 and less than 600, and more typically more than 250 and less than 550.

One aspect of the invention, relates to compounds of general formula XXIX and salts thereof:



(XXIX)

wherein **f, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}** and **$R^{12'}$**are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XXIX.

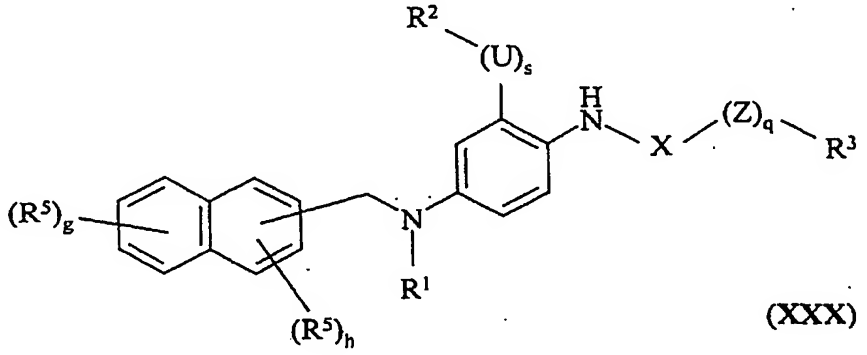
In another embodiment, the invention relates to compounds of the general formula XXIX, wherein **f** is 0.

In another embodiment, the invention relates to compounds of the general formula XXIX being substituted by one substituent **R^5**, such as in the ortho-, meta- or para-position.

In yet another embodiment, the invention relates to compounds of the general formula XXIX being substituted by two independently selected **R^5** substituents, such as in the ortho- and para-position, in the metha- and para-position and in the orto- and meta-position.

In yet another embodiment, the invention relates to compounds of the general formula XXIX being substituted by three independently selected **R^5** substituents.

Another aspect of the invention relates to compounds of the general formula XXX or salts thereof:



(XXX)

wherein **g, h, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}** and **$R^{12'}$**are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XXX.

In an embodiment, the invention relates to compounds of the general formula XXX, wherein the nitrogen atom is attached to position 1 of the naphtyl group.

In another embodiment, the invention relates to compounds of the general formula XXX, wherein the nitrogen atom is attached to position 2 of the naphtyl group.

In yet another embodiment, the invention relates to compounds of the general formula XXX, wherein **g** is 0, 1, 2 or 3, typically 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XXX, wherein **h** is 0, 1 or 2, typically 0 or 1.

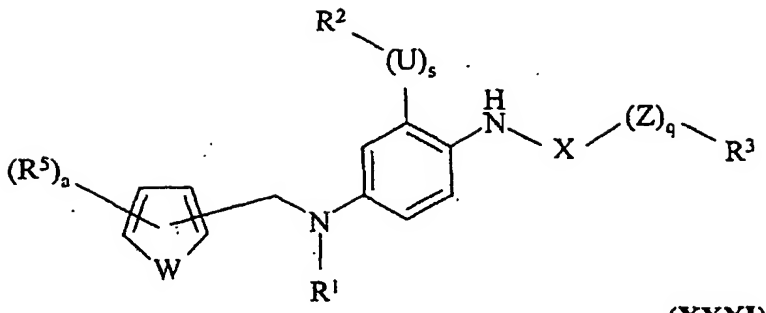
In yet another embodiment, the invention relates to compounds of the general formula XXX, wherein both **g** and **h** are 0.

In yet another embodiment, the invention relates to compounds of the general formula XXX being substituted by one substituent $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XXX being substituted by two independently selected $\mathbf{R^5}$ substituents.

In yet another embodiment, the invention relates to compounds of the general formula XXX being substituted by three independently selected $\mathbf{R^5}$ substituents.

Yet another aspect of the invention relates to compounds of the general formula XXXI or salts thereof:



(XXXI)

wherein **a**, **s**, **q**, **U**, **W**, **X**, **Z**, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12} and $R^{12'}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XXXI.

In an embodiment, the invention relates to compounds of the general formula XXXI, wherein the nitrogen atom is attached to position 2 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XXXI, wherein the nitrogen atom is attached to position 3 of the heteroaromatic group.

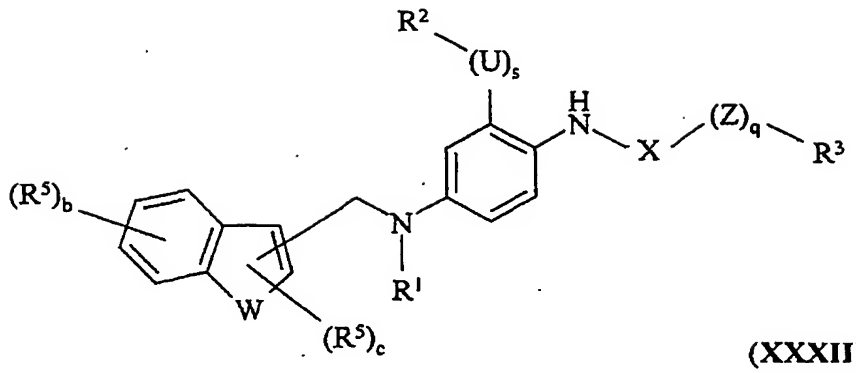
In yet another embodiment, the invention relates to compounds of the general formula XXXI, wherein **a** is 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XXXI, wherein **a** is 0.

In yet another embodiment, the invention relates to compounds of the general formula XXXI being substituted by one substituent R^5.

In yet another embodiment, the invention relates to compounds of the general formula XXXI being substituted by two independently selected R^5 substituents.

Yet another aspect of the invention relates to compounds of the general formula XXXII or salts thereof:



(XXXII)

wherein **b**, **c**, **s**, **q**, **U**, **W**, **X**, **Z**, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12} and $R^{12'}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XXXII.

In an embodiment, the invention relates to compounds of the general formula XXXII, wherein the nitrogen atom is attached to position 2 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XXXII, wherein the nitrogen atom is attached to position 3 of the heteroaromatic group.

In yet another embodiment, the invention relates to compounds of the general formula XXXII, wherein **b** is 0, 1, 2 or 3, typically 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XXXII, wherein **c** is 0 or 1, typically 0.

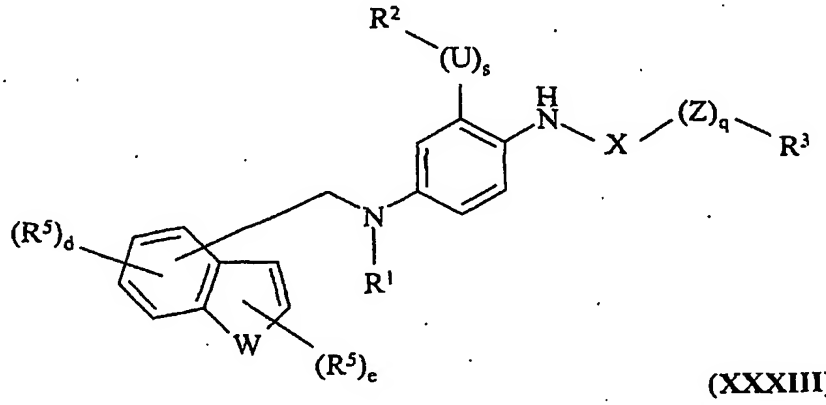
In yet another embodiment, the invention relates to compounds of the general formula XXXII, wherein both **b** and **c** are 0.

In yet another embodiment, the invention relates to compounds of the general formula XXXII being substituted by one substituent R^5.

In yet another embodiment, the invention relates to compounds of the general formula XXXII being substituted by two independently selected R^5 substituents.

In yet another embodiment, the invention relates to compounds of the general formula XXXII being substituted by threee independently selected R^5 substituents.

Yet another aspect of the invention relates to compounds of the general formula XXXIII or salts thereof:



(XXXIII)

wherein **d, e, s, q, U, W, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}** and **$R^{12'}$** are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XXXIII.

In an embodiment, the invention relates to compounds of the general formula XXXIII, wherein the nitrogen atom is attached to position 4 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XXXIII, wherein the nitrogen atom is attached to position 5 of the heteroaromatic group.

In an embodiment, the invention relates to compounds of the general formula XXXIII, wherein the nitrogen atom is attached to position 6 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XXXIII, wherein the nitrogen atom is attached to position 7 of the heteroaromatic group.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII, wherein **d** is 0, 1 or 2, typically 0 or 1.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII, wherein **e** is 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII, wherein both **d** and **e** are 0.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII being substituted by one substituent $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII being substituted by two independently selected $\mathbf{R^5}$ substituents.

In yet another embodiment, the invention relates to compounds of the general formula XXXIII being substituted by three independently selected $\mathbf{R^5}$ substituents.

The compounds of the following list and salts thereof are preferred:

1a *{4-[(Benzofuran-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester*

1b *{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester*

1c *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester.*

1d *{2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester.*

1e *[4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid ethyl ester*

1f *[4-(4-Fluoro-benzylamino)-2-methylphenyl]-carbamic acid propyl ester*

1g *(4-{[4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-2-methylphenyl)-carbamic acid propyl ester*

1h *{4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester*

1i *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester*

1j {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester

1k {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester

1l {2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

1m [4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid propyl ester

1o {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1p {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1q {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1r [2-Chloro-4-(4-isopropyl-benzylamino)-phenyl]-carbamic acid ethyl ester

1s [2-Chloro-4-(4-fluoro-benzylamino)-phenyl]-carbamic acid propyl ester

1t 2-Chloro-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid propyl ester

1u {4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1v {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1w {2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

1x {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1y {4-[(Benzofuran-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1z {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid ethyl ester

1aa {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid methyl ester

1ab {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid isopropyl ester

2a {4-[(4-Fluoro-benzyl)-(methyl)amino]-2-methoxyphenyl}-carbamic acid propyl ester

2b [4-(Benzo[b]thiophen-2-ylmethyl-(methyl)amino)-2-methoxy-phenyl]-carbamic acid propyl ester

2c {4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester

2d {4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester

2e {2-Methoxy-4-[methyl-(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

3a {4-[(4-Fluorobenzyl)-(methyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester

4a [4-(3-Fluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester

4b [4-(4-Isopropylbenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester

4c {2-Methoxy-4-[(3-methylthiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester

4d [4-(2,4-Difluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester

5a [2-Cyclopentyloxy-4-(4-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester

5b [2-Cyclopentyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester

5c [4-(3-Fluoro-2-methylbenzylamino)-2-phenethyloxyphenyl]-carbamic acid ethyl ester

5d [2-Benzyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester

5e [2-Benzyloxy-4-(4-methylsulfanylbenzylamino)-phenyl]-carbamic acid ethyl ester

5f {4-[(Benzo[b]thiophen-3-ylmethyl)-amino]-2-cyclopentyloxyphenyl}-carbamic acid ethyl ester

5g [4-(3-Fluoro-2-methylbenzylamino)-2-isopropoxyphenyl]-carbamic acid ethyl ester

5h [2-Benzyloxy-4-(3-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester

5i {4-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester.

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Cyano-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-carbamic acid propyl ester

{4-[(4-Isopropylbenzyl)-(methyl)amino]-2-methylphenyl}-carbamic acid propyl ester

{2-Methyl-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Methyl-4-[methyl-(4-methylsulfanyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid ethyl ester

{2-Chloro-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid ethyl ester

{2-Chloro-4-[methyl-(4-methylsulfanyl-benzyl)-amino]-phenyl}-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid propyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid propyl ester

{2-Chloro-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(4-Isopropyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[Methyl-(4-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[Methyl-(4-methylsulfanyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-methyl-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(4-Isopropyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(4-tert!-Butyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[Methyl-(4-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[Methyl-(4-methylsulfanyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-cyanophenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-cyanophenyl}-carbamic acid propyl ester

{2-Cyano-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-bromo-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(4-isopropylbenzyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(4-tert-butyl-benzyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Iodo-4-(4-isopropyl-benzylamino)-phenyl]-carbamic acid propyl ester

[4-(4-tert-Butyl-benzylamino)-2-iodophenyl]-carbamic acid propyl ester

[2-Iodo-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Iodo-4-(4-methylsulfanyl-benzylamino)-phenyl]-carbamic acid propyl ester

{2-Iodo-4-[4-(4-methylpiperazin-1-yl)-benzylamino]-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

[4-(4-tert-Butyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid ethyl ester

[4-(4-Methylsulfanyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

[4-(4-Isopropylbenzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[4-(4-tert-Butyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[2-Trifluoromethyl-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[4-(4-Dimethylamino-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[4-(4-Methylsulfanyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid propyl ester

[2-Cyano-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

{2-Bromo-4-[(5-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Bromo-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-tert-butyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-methylsulfanyl-benzylamino)-phenyl]-carbamic acid propyl ester

N-{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-butyramide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-butyramide

N-[4-(4-Isopropylbenzylamino)-2-methoxyphenyl]-butyramide

N-[4-(4-tert-Butyl-benzylamino)-2-methoxyphenyl]-butyramide

N-[2-Methoxy-4-(4-trifluoromethyl-benzylamino)-phenyl]-butyramide

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-furan-2-yl-phenyl}-carbamic acid propyl ester

[2-Furan-2-yl-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid propyl ester

[5-(4-Fluorobenzylamino)-biphenyl-2-yl]-carbamic acid propyl ester

{5-[(5-Chloro-thiophen-2-ylmethyl)-amino]-biphenyl-2-yl}-carbamic acid propyl ester

[5-(4-Isopropylbenzylamino)-biphenyl-2-yl]-carbamic acid propyl ester

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-phenylacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3,3-dimethylbutyramide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-phenylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-butyramide

Pentanoic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclopropanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclobutanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclopentanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclohexanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-thiophen-2-yl-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(3-methoxy-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-chloro-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-methoxy-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-fluoro-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-cyclohexylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2-dimethylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-phenoxyacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-phenylacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-3,3-dimethylbutyramide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-butyramide

Pentanoic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclopropanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclobutanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclopentanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclohexanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-thiophen-2-yl-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(3-methoxyphenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-chlorophenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-methoxyphenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-fluorophenyl)-acetamide

2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

2,3-Dihydro-benzofuran-5-carboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-3-cyclohexylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-2,2-dimethylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-2-phenylacetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-3,3-dimethylbutyramide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-3-phenylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-butyramide

2,2,2-Trichloro-N-{4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-acetamide

Cyclopropanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-amide

Cyclobutanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

Cyclopentanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

Cyclohexanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-thiophen-2-yl-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(3-methoxyphenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-malonamic acid methyl ester

2-(4-Chlorophenyl)-N-{4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(4-methoxyphenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(4-fluorophenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-3-cyclohexylpropionamide

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid phenyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid benzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid isobutyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid butyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid hexyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 4-nitrobenzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid but-3-enyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid but-2-ynyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2,2-dimethylpropyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2-chlorobenzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 3-chloropropyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2-benzyloxyethyl ester

3-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-1-methyl-1-propyl-urea

1-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-(2-fluorophenyl)-urea

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2,2,2-trifluoroacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2,2-trifluoroacetamide

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula I wherein **a, b, c, d, e, f, g, h, s, q, U, X, Z, Y, W, R^1, $R^{1'}$, R^2,**

$R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12} and $R^{12'}$ are as defined under formula I, or salts thereof.

The invention provides a pharmaceutical composition for oral or parenteral administration, said pharmaceutical composition comprising at least one compound of formula I or a salt thereof in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

In one aspect, the compounds of the invention may be administered as the only therapeutically effective compound.

In another aspect the compounds of the invention may be administered as a part of a combination therapy, i.e. the compounds of the invention may be administered in combination with other therapeutically effective compounds having e.g. anti-epileptic properties. The effects of such other compounds having anti-epileptic properties may include but not be limited to activities on:

- ion channels such as sodium, potassium, or calcium channels
- the excitatory amino acid systems e.g. blockade or modulation of NMDA receptors
- the inhibitory neurotransmitter systems e.g. enhancement of GABA release, or blockade of GABA-uptake and/or
- membrane stabilisation effects.

Current antiepileptic medications include, but are not limited to, tiagabine, carbamazepine, sodium valproate, lamotrigine, gabapentin, pregabalin, ethosuximide, levetiracetam, phenytoin, topiramate, zonisamide as well as members of the benzodiazepine and barbiturate class.

In one aspect, the compounds of the invention have been found to have effect on potassium channels of the KCNQ family, in particular the KCNQ2 subunit.

The compounds of the invention are considered useful for increasing ion flow in a voltage-dependent potassium channel.

The compounds of the invention are considered useful for the prevention, treatment or inhibition of a disorder or condition being responsive to an increased ion flow in a potassium channel such as the KCNQ family potassium ion channels.

Accordingly, the compounds of the invention are considered useful for the prevention, treatment or inhibition of disorders or conditions such as convulsions, epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.

Accordingly, the compounds of the invention are considered useful in the prevention, treatment and inhibition of convulsions.

Accordingly, the compounds of the invention are considered useful in the prevention, treatment and inhibition of epilepsy, epileptic syndromes and epileptic seizures.

The compounds of the invention are further considered useful in the prevention, treatment and inhibition of anxiety disorders such as conditions and diseases related to panic attack, agoraphobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorders, generalized anxiety disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, separation anxiety disorder, adjustment disorders and anxiety disorder not otherwise specified.

The compounds of the invention are also considered useful in the prevention, treatment and inhibition of neuropathic pain such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neupathic pain related to migraine.

Additionally, the compounds of the invention are considered useful in the prevention, treatment and inhibition of neurodegenerative disorders such as alzheimer's disease; huntington's chorea; multiple sclerosis; amyotrophic lateral sclerosis; Creutzfeld-Jakob disease; Parkinson's disease; encephalopathies induced by AIDS or infection by rubella viruses, herpes viruses, borrelia and unknown pathogens; trauma-induced neurodegenerations; neuronal hyperexcitation states such as in medicament

withdrawal or intoxication; and neurodegenerative diseases of the peripheral nervous system such as polyneuropathies and polyneuritides.

According to one particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 10000nM.

According to one particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 2000nM.

According to another particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 200nM.

Definitions

The term heteroatom refers to a nitrogen, oxygen or sulphur atom.

Halogen means fluoro, chloro, bromo or iodo.

The expressions C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yl mean a C_{1-6}-alkyl, C_{2-6}-alkenyl or a C_{2-6}-alkynyl group.

The term C_{1-6}-alkyl refers to a branched or un-branched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6}-alkenyl and C_{2-6}-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The expression C_{1-3}-alk(en/yn)yl means a C_{1-3}-alkyl, C_{2-3}-alkenyl or a C_{2-3}-alkynyl group.

The term C_{1-3}-alkyl refers to a branched or un-branched alkyl group having from one to three carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl and 2-propyl.

Similarly, C_{2-3}-alkenyl and C_{2-3}-alkynyl, respectively, designate such groups having from two to three carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, ethynyl and propynyl.

The expressions C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(an/en)yl mean a C_{3-8}-cycloalkyl- or cycloalkenyl group.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The expressions C_{3-6}-cycloalk(en)yl and C_{3-6}-cycloalk(an/en)yl mean a C_{3-6}-cycloalkyl- or cycloalkenyl group.

The term C_{3-6}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to six C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8}-cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

The term heterocycloalk(en)yl designates a monocyclic or bicyclic ring systems wherein the ring is formed by 5 to 8 atoms being selected from the group consisting of carbonatoms and heteroatoms; with the proviso that one or two of the ring forming atoms are independently selected heteroatoms.

The term halo-C_{1-6}-alk(en/yn)yl designates C_{1-6}-alk(en/yn)yl being substituted with one or more halogen atoms, including but not limited to trifluoromethyl. Similarly, halo-C_{3-8}-cycloalk(en)yl designates C_{3-8}-cycloalk(en)yl being substituted with one or more halogen atoms and halo-heterocycloalk(en)yl designates heterocycloalk(en)yl being substituted with one or more halogen atoms.

As used herein, the term acyl refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl, Ar-carbonyl, Ar-C_{1-6}-alk(en/yn)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group, wherein C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and Ar are as defined above.

When two substituents together with a nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom, then a monocyclic ring system is formed by 5 to 8 atoms, one or two of said atoms are heteroatoms. Examples of such ring systems are pyrrolidine, piperidine, piperazine, morpholine, pyrrole, oxazolidine, thiazolidine, imidazolidine, tetrazole and pyrazole.

When two adjacent substituents together with an aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms, then a ring of 5-8 atoms is formed, said ring is fused to the aromatic group. Such two adjacent substituents may together form:
$-(CH_2)_{n''}-CH_2-$, $-CH=CH-(CH_2)_{m''}-$, $-CH_2-CH=CH-(CH_2)_{p''}$, $-CH=CH-CH=CH-$, $-(CH_2)_{n''}-O-$, $-O-(CH_2)_{m''}-O-$, $-CH_2-O-(CH_2)_{p''}-O-$, $-CH_2-O-CH_2-O-CH_2-$, $-(CH_2)_{n''}-S-$, $-S-(CH_2)_{m''}-S-$, $-CH_2-S-(CH_2)_{p''}-S-$, $-CH_2-S-CH_2-S-CH_2-$, $-(CH_2)_{n''}-NH-$, $-NH-(CH_2)_{m''}-NH-$, $-CH_2-NH-(CH_2)_{p''}-NH-$, $-CH=CH-NH-$, $-O-(CH_2)_{m''}-NH-$, $-CH_2-O-(CH_2)_{p''}-NH-$ or $-O-(CH_2)_{p''}-NH-CH_2-$, $-S-(CH_2)_{m''}-NH-$, $-N=CH-NH-$, $-N=CH-O-$ or $-N=CH-S-$, wherein m'' is 1, 2 or 3, n'' is 2, 3 or 4 and p'' is 1 or 2.

The term Ar refers to optionally substituted aromatic systems of 5-10 carbon atoms, wherein 0, 1, 2, 3 or 4 carbon atoms may be replaced with independently selected heteroatoms. Examples of such Ar groups are optionally substituted phenyl, naphtyl, pyridine, thiophene, furan thiazole and oxazole. Ar may be substituted with one or more substituents independently being hydroxy, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-alk(en/yn)yloxy, acyl, nitro or cyano, -CO-NH-C_{1-6}-alk(en/yn)yl, -CO-N(C_{1-6}-alk(en/yn)yl)$_2$, -NH-C_{1-6}-alk(en/yn)yl, -N(C_{1-6}-alk(en/yn)yl)$_2$, -S- C_{1-6}-alk(en/yn)yl, $-SO_2-C_{1-6}$-alk(en/yn)yl and $-SO_2O-C_{1-6}$-

alk(en/yn)yl; or two adjacent substituents may together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

The terms C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{3-8}-cycloalk(en)yloxy, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-alk(en/yn)ylcarbonyl, Ar-carbonyl, Ar-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)ylcarbonyl, -CO-C_{1-6}-alk(en/yn)yl, -S-C_{1-6}-alk(en/yn)yl, -SO_2-C_{1-6}-alk(en/yn)yl and -SO_2O-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, acyl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar, halo-heterocycloalk(en)yl-Ar, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl etc. designate such groups in which the C_{1-6}-alk(en/yn)yl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalk(en)yl, heterocycloalk(en)yl, Ar, cyano, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl and acyl are as defined above.

The salts of the invention are preferably pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts.

Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric and nitric acids and the like.

Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, ethanesulfonic, tartaric, ascorbic, pamoic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, itaconic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline.and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The compounds of this invention may exist in unsolvated as well as in solvated forms with solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formulas I, XXIX, XXX, XXXI, XXXII or XXXIII, which are readily convertible in vivo into the required compound of the formulas I, XXIX, XXX, XXXI, XXXII or XXXIII. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

Whenever mentioned in relation to the compounds of the formulas I, XXIX, XXX, XXXI, XXXII or XXXIII, the terms epilepsy and epilepsies embrace any of the epilepsies, epileptic syndromes and epileptic seizures referred to in International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* **1981** 22: 489-501 and in International League Against Epilepsy: Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* **1989** 30(4): 389-399.

Whenever mentioned in relation to the compounds of the formulas I, XXIX, XXX, XXXI, XXXII or XXXIII, the term anxiety disorders embraces conditions and diseases related to panic attack, agoraphobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorders, generalized anxiety disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, separation anxiety disorder, adjustment disorders and anxiety disorder not otherwise specified as defined by American Psychiatric Association *Diagnostic and statistical manual of mental disorders*, 4ed **1994**: 110-113, 393-444 and 623-627.

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is a base addition salt of a compound having the utility of a free acid. When a compound of the invention contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of a free acid of the compound of the invention with a chemical equivalent of a pharmaceutically acceptable base. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to a desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents.

Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc; agar, pectin, acacia, stearic acid and lower alkyl ethers of cellulose corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like.

Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical compositions formed by combining the novel compounds of the invention and the pharmaceutical acceptable carriers are then readily administered in a

variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include one or more suitable excipients. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tablette, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula I, XXIX, XXX, XXXI, XXXII or XXXIIIin combination with further pharmacologically active substances such as those described in the foregoing.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of a compound of the invention calculated as the free base:

Compound of formula I, XXIX, XXX, XXXI, XXXII or XXXIII		5.0 mg
Lactose	60 mg	
Maize starch	30 mg	

Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound of formula I, XXIX, XXX, XXXI, XXXII or XXXIII 0.5 mg

Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

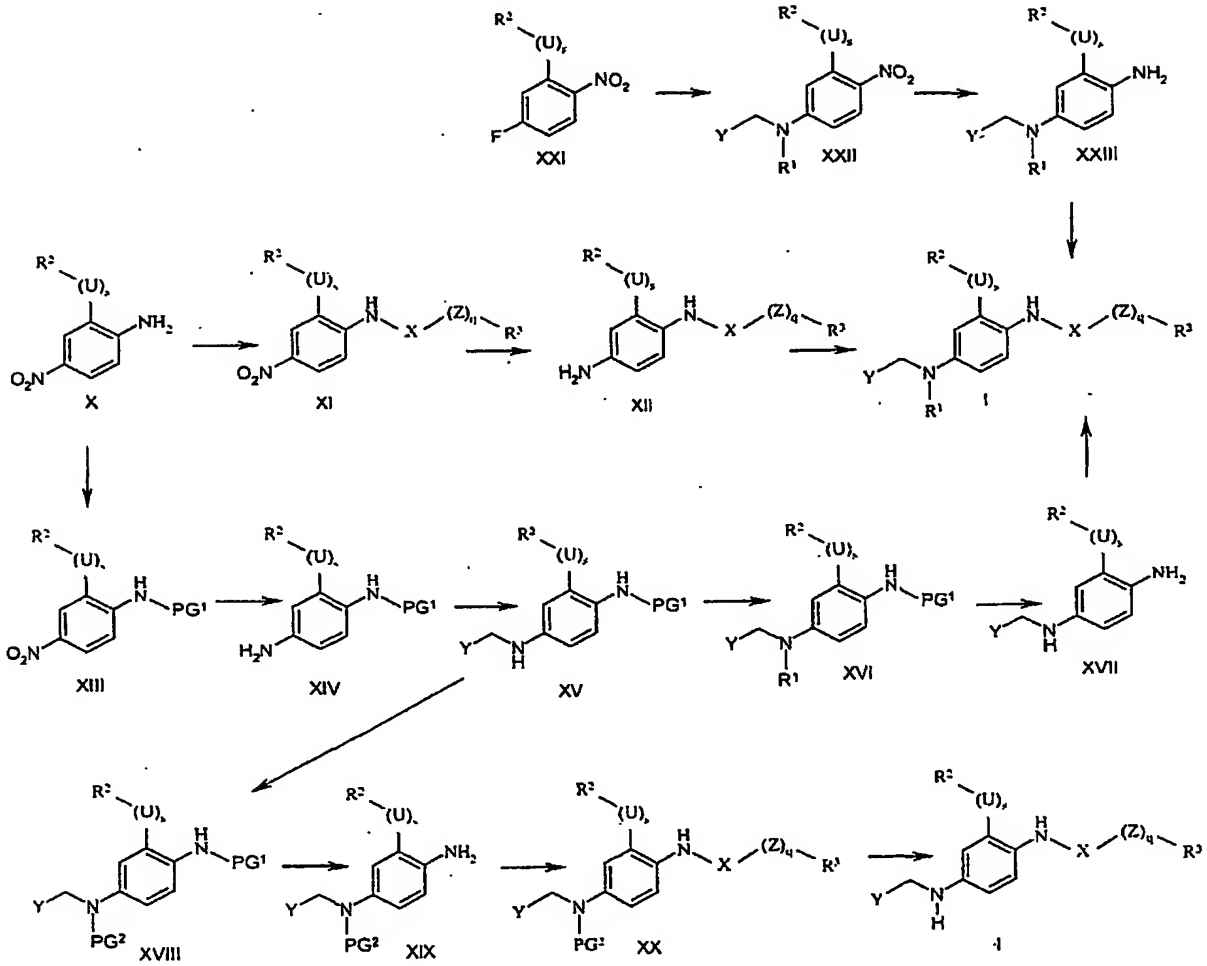
Compound of formula I, XXIX, XXX, XXXI, XXXII or XXXIII	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 mL
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

4) Solution for injection containing per millilitre:

Compound of formula I, XXIX, XXX, XXXI, XXXII or XXXIII	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg

Water

Preparation of the compounds of the invention



The compounds of the invention of the general formula I, wherein **a, b, c, d, e, f, g, h, s, q, U, W, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}** and **$R^{12'}$** are defined under formula I are prepared by the methods as described below and as represented in the scheme.

Substituted 4-nitroanilines of the general formula **X** or **XI** are commercially available, described in the literature or prepared according to methods known to chemists skilled in the art. In particular, compounds of the general formula **X** or **XI** with s being 0 and R^2 being substituted aryl or substituted heteroaryl as defined above such as furanyl, thienyl, phenyl, pyridinyl can be prepared from corresponding compounds with R^2 being I or Br by means of cross-coupling reactions known to chemists skilled in the

art, such as *Suzuki* coupling, *Stille* coupling, or other transition metal catalyzed cross-coupling reactions [D.W. Knight "Coupling Reactions Between sp2 Carbon Centers" in *Comprehensive Organic Synthesis*, v. 3, pp. 481-520, Pergamon Press 1991]. Alternatively, 4-nitroanilines with the general formula **X** or **XI** can be prepared from the corresponding 2-substituted aniline in the protected or unprotected form by nitration known to chemists skilled in the art [R. Behnisch " Aromatische Nitro-Verbindungen" in *Methoden der Organische Chemie/(Houben-Weyl)* p. 255, v. E16d, Thieme: 1992]. In particular, this method can be applied for compounds with the general formula **X** or **XI** where U is S, SO_2, or SO_2NR^{11}. Also, compounds of the general formula **X** or **XI** where U is S can be converted into compounds of the general formula **X** or **XI** where U is SO_2 by oxidation according to methods known to the chemist skilled in the art, for example by oxidation with 3-chloroperoxybenzoic acid or $NaIO_4$ in the presence of $RuCl_3$ as a catalyst.

Compounds of the general formula **XI** are also prepared from compounds of general formula **X** by the reaction with suitable electrophilic reagents forming an R^3-$(Z)_q$-X group, such as chloroformiates, acid anhydrides, acid fluorides, acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, or isocyanates in suitable solvents, such as acetonitrile, tetrahydrofuran, 1,2-dichloroethane, or methylene chloride, at suitable temperature, such as room temperature or reflux, with or without addition of bases, such magnesium oxide, potassium carbonate, sodium hydride, trialkylamines, sodium- or potassium alcoholates, or pyridine, reactions well known to the chemist skilled in the art.

Additionally, for further variation of R^2, compounds of the general formula **XI**, wherein R^2 is methyl, U is oxygen, and s is 1, can be demethylated by methods known to chemists skilled in the art, such as treatment with boron tribromide in a suitable solvent, such as dichloromethane, at a suitable temperature, such as 0 °C or room temperature. The resulting phenols can then be transformed into compounds of the general formula **XI**, wherein U is oxygen, and s is 1, by methods known to chemists skilled in the art. Such methods include: (a) the reaction with electrophiles, such as alkyl chlorides, alkyl bromides, alkyl iodides, benzyl chlorides, benzyl bromides, benzyl iodides, carbonic acid chlorides, carbonic acid bromides, or carbonic acid anhydrides in the presence of suitable bases, such as potassium carbonate, in a

suitable solvent, such as tetrahydrofuran, *N,N*-dimethylformamide, or 1,2-dichloroethane, at suitable temperatures, such as room temperature or reflux temperature; (b) the reaction with alkyl, benzylic, or heteroarylalkyl alkohols under conditions known as the *Mitsunobu* reaction (O. Mitsunobu *Synthesis* **1981**, 1).

The nitro group in compounds of the general formula **XI** can be reduced with suitable reducing agents such as zinc or iron powder in the presence of acid such as acetic acid or aqueous hydrochloric acid, or hydrogen gas or ammonium formiate in the presence of suitable hydrogenation catalyst such as palladium on activated carbon in suitable solvents such as methanol, ethanol, or tetrahydrofuran, at suitable temperatures or under ultrasonic irradiation, to obtain anilines with the general formula **XII**. Alternatively, tin (II) chloride or sodium dithionite can be used as reducing agents under conditions well known to the chemist skilled in the art.

Obtained anilines with the general formula **XII** are subjected to reductive alkylation reactions, known to chemists skilled in the art, with aldehydes of the general formula YCHO where Y is defined as above in suitable solvents such as methanol, ethanol, xylene, tetrahydrofuran, or mixtures thereof, at suitable temperatures with the formation of intermediate imines which can be reduced *in situ* or can be separated by evaporation of the solvent or crystallisation. They are reduced to the compounds of the invention of the general formula **I**, where R^1 is hydrogen, with reducing agents, such as sodium borohydrate or sodium cyanoborohydrate, in a suitable solvent, such as ethanol, methanol or acetonitrile with or without addition of catalytic amounts of acid, such as acetic acid, at suitable temperatures.

Optionally, for variation of R^1, the obtained compounds of the general formula **I** where R^1 is hydrogen can be further derivatized by the second reductive alkylation procedure using suitable aldehydes and reducing agents such as sodium cyanoborohydrate, as described above. This procedure can be performed *in situ* after the first reductive alkylation with aldehydes of the general formula YCHO. Alternatively, R^1 can be introduced by the electrophilic substitution reaction with the appropriate electrophiles of the general formula R^1-LG, where LG is a suitable leaving group such as iodide, bromide, or sulphonate under conditions known to the chemist skilled in the art.

For the further variation of R^3, Z and X, the compounds of the invention with the general formula **I** can be obtained by an alternative route:

Compounds with the general formula **XIII** are prepared by protection of the aniline nitrogen in the substituted 4-nitro anilines with the general formula **X** with an appropriate protecting group (PG^1) [*Protective Groups in Organic Synthesis*, 3rd Edition T. W. Greene, P. G. M. Wuts, Wiley Interscience 1999], such as a trifloroacetyl group known to chemists skilled in the art as TFA group, by reaction with the reagent forming the protective group such as trifluoroacetic acid anhydride in a suitable solvent, such as 1,2-dichloroethane at appropriate temperatures.

Anilines with the general formula **XIV** are obtained by reduction of the nitro group according to methods known to chemists skilled in the art, as described above. Then they are subjected to the reductive alkylation reactions as described above, with the aldehydes of the general formula YCHO to furnish compounds with the general formula **XV**.

Compounds with the general formula **XV** are subjected to the second reductive alkylation step, as described above, to furnish compounds with the general formula **XVI**, where PG^1 is TFA. Then the TFA group can be removed by methods known to chemists skilled in the art, such as hydrolysis with aqueous potassium carbonate in an appropriate solvent, such as methanol, at a suitable temperature, furnishing compounds of the general formula **XVII**.

The compounds of the invention with the general formula **I** where R^1 is not hydrogen are obtained from anilines with the general formula **XVII** by the reaction with suitable electrophilic reagents forming forming R^3-$(Z)_q$-X group such as alkyl, aryl or heteroaryl chloroformiates or carbamyl chlorides, acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, isocyanates, carbonic acid anhydrides, activated carbonic acids with activating reagents such as carbodiimides or others as known to chemists skilled in the art, in the suitable solvents, such as acetonitrile, tetrahydrofuran, 1,2-dichloroethane, or methylene chloride at a suitable temperature, such as room

temperature or reflux, with or without addition of bases, such as magnesium oxide, potassium carbonate, trialkylamines, or pyridine, as descibed above.

For the compounds of the invention with general formula **I** wherein R^1 is hydrogen, compounds with the general formula **XV** are subjected to the protection with appropriate protective group (PG^2), known to chemists skilled in the art [*Protective Groups in Organic Synthesis*, 3rd Edition T. W. Greene, P. G. M. Wuts, Wiley Interscience 1999], to furnish compounds with the general formula **XVIII**. In particular, compounds of the general formula **XVIII** where PG^2 is *tert*-butylcarbonyl group, known to chemists skilled in the art as Boc group, can be prepared with the appropriate reagent forming protective group such as *tert*-butyl carbonic acid anhydride in an appropriate solvent such as acetonitrile and at appropriate temperature such as +80°C, to furnish compounds of the general formula **XVIII** where PG^2 is Boc. Then the TFA protective group (PG^1) is removed, as described above, to furnish compounds with the general formula **XIX**, followed by derivatisation with appropriate electrophiles forming R^3-$(Z)_q$-X group to furnish compounds with the general formula **XX**, as described above.

Finally, the compounds of the invention with general formula **I** wherein R^1 is hydrogen are obtained from the compounds with the general formula **XX** by means of deprotection of PG^2 by the methods known to chemists skilled in the art. In particular, the Boc protective group can be cleaved by the methods known to chemists skilled in the art such as deprotection with an appropriate acid, for example trifluoroacetic acid, in the absence or presence of solvent such as methylene chloride or toluene at appropriate temperatures.

Alternatively, compounds of the general formula **I** can be prepared by a route as follows:

Compounds of the general formula **XXI** , wherein R^2, U, and s are as defined above, are commercially available or prepared by methods known to the chemist skilled in the art. These include the reactions of 5-fluoro-2-nitrophenol under *Mitsunobu*-, alkylation- or acylation conditions as described above for the synthesis of compounds of the general formula **XI** from phenols. Nucleophilic aromatic substitution with amines of the type Y-CH_2-NH-R^1, a reaction well known to chemists skilled in the art,

furnishes compounds with the general formula **XXII**. Compounds with the general formula **XXIII** are prepared by the reduction of the nitro group, carried out under the conditions as described above for the synthesis of compounds of the general structures **XII**. The reaction of compounds with the the general formula **XXIII** with suitable electrophilic reagents forming an R^3-$(Z)_q$-X group, as described above for compounds of the general formula **XI**, furnishes the compounds of the invention with the general formula **I**.

Examples

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.

Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 minutes and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz and ^{13}C NMR spectra were recorded at 125.76 MHz, both on a Bruker Avance DRX500 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

Preparation of intermediates

N-(*p*-Fluorobenzyl)-methylamine was synthesised according to the procedure described by G. M. Singer and A. W. Andrews *J. Med. Chem.* **1983**, *26*, 309.

Preparation of intermediates of the general formula XI

(2-Chloro-4-nitrophenyl)-carbamic acid ethyl ester.

A suspension of MgO (2.0 g), 2-chloro-4-nitroaniline (3.768 g, 21.83 mmol) and ethyl chloroformate (5 ml) in acetonitrile (25 ml) was heated to reflux temperature for 4 hours followed by addition of more ethyl chloroformate (4 ml). The heating was continued until full conversion (20 hours) then the reaction mixture was filtered via a plug of SiO_2 (5 g) with ethyl acetate as an eluent. Evaporation in vacuo (50°C) gave 5.8 g (100% yield) of crude title compound which was used in the next step without further purification. LC/MS (m/z) 245 ($[M+H]^+$); RT = 2.95, (UV, ELSD) 96%, 98.5%. ^{1}H NMR (DMSO-d_6): 1.27 (t, 3H); 4.19 (q, 2H), 8.06 (d, 1H), 8.19 (dd, 1H), 8.30 (d, 1H), 9.49 (s, NH).

The following compounds were prepared analogously using appropriate chloroformates:

(2-Chloro-4-nitrophenyl)-carbamic acid propyl ester.

Propyl chloroformate and tetrahydrofuran were used instead. The title compound was crystallized by addition of diisopropyl ether to the crude product and separated by filtration. Yield 3.3 g (62%), colorless solid. ^{1}H NMR (DMSO-d_6): 0.94 (t, 3H); 1.67 (m, 2H), 4.10 (t, 2H), 8.06 (d, 1H), 8.20 (dd, 1H), 8.31 (d, 1H), 9.52 (s, NH).

(4-Nitrophenyl)-carbamic acid propyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(4-Nitrophenyl)-carbamic acid ethyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(2-Methoxy-4-nitrophenyl)-carbamic acid methyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(2-Methoxy-4-nitrophenyl)-carbamic acid isopropyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(2-Methoxy-4-nitrophenyl)-carbamic acid propyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(2-Methoxy-4-nitrophenyl)-carbamic acid 4-fluorophenyl ester.

Reaction was performed at room temperature in acetone as a solvent. The product was used in the next step without purification.

(2-Methyl-4-nitrophenyl)-carbamic acid ethyl ester.

The crude product was used in the next step without further purification. RT = 2.69, (UV, ELSD) 75%, 99.7%.

(2-Methyl-4-nitrophenyl)-carbamic acid propyl ester.

The crude product was used in the next step without further purification. RT = 2.97, (UV, ELSD) 62%, 99.7%.

(2-Bromo-4-nitrophenyl)-carbamic acid propyl ester.

The crude product was purified by crystallisation from ethyl acetate - hexane. ^{1}H NMR (DMSO-d_6): 0.94 (t, 3H), 1.66 (m, 2H), 4.10 (t, 2H), 7.97 (d, 1H), 8.23 (dd, 1H), 8.44 (d, 1 H), 9.28 (br. s, NH).

(2-Iodo-4-nitrophenyl)-carbamic acid propyl ester.

The crude product was purified by crystallisation from ethyl acetate - hexane. Pale yellow needles. ^{1}H NMR (DMSO-d_6): 0.94 (t, 3H), 1.66 (m, 2H), 4.09 (t, 2H), 7.79 (d, 1H), 8.24 (dd, 1H), 8.60 (d, 1H), 9.07 (br. s, NH). LC/MS (m/z) 335.0 ($[M-O]^+$), RT = 3.40, (UV, ELSD) 99%, 100%.

(4-Nitro-2-cyanophenyl)-carbamic acid propyl ester.

Sodium hydride was used instead as a base prior to addition of propyl chloroformate at room temperature. The crude product contaminated with double acylation product

was treated with aqueous $NaHCO_3$ in methanol for 16 hours and purified by flash chromatography. ^1H NMR ($CDCl_3$): 1.01 (t, 3H), 1.76 (m, 2H), 4.22 (t, 2H), 7.47 (br. s, 1H, NH), 8.43 (dd, 1H), 8.47 (d, 1H), 8.57 (d, 1H).

The following compounds were prepared analogously:

(4-Nitro-2-cyanophenyl)-carbamic acid ethyl ester.
^1H NMR (DMSO-d_6): 1.28 (t, 3H), 4.21 (q, 2H), 7.88 (d, 1H), 8.47(dd, 1H), 8.68 (d, 1H), 10.34 (s, 1H, NH). LC/MS (m/z) 220.1 ($[M+H]^+$), RT = 2.46, (UV, ELSD) 97%, 98%.

(2-Trifluoromethyl-4-nitrophenyl)-carbamic acid propyl ester.
^1H NMR ($CDCl_3$): 1.00 (t, 3H), 1.75 (m, 2H), 4.20 (t, 2H), 7.26 (br. s, 1H, NH), 8.41 (dd, 1H), 8.50 (d, 1H), 8.57 (d, 1H).

(2-Trifluoromethyl-4-nitrophenyl)-carbamic acid ethyl ester.
^1H NMR ($CDCl_3$): 1.37 (t, 3H), 4.31 (q, 2H), 7.25 (br. s, 1H, NH), 8.41 (dd, 1H), 8.50 (d, 1H), 8.57 (d, 1H).

N-(2-Methoxy-4-nitrophenyl)-butyramide.
To a cold (ice/water bath) solution of 2-methoxy-4-nitroaniline (4.00 g, 23.8 mmol) in acetonitrile (40 ml) and triethylamine (5 ml) butyryl chloride (2.66 g, 25 mmol) was added. After 30 min the obtained suspension was poured into saturated aqueous $NaHCO_3$ (300 ml). After sonication for 10 min the title compound was separated by filtration as a yellow-brown solid, washed with water and dried in vacuo. Yield 5.34 g, 94%. LC/MS (m/z) 238.9 ($[M+H]^+$), RT = 2.69, (UV, ELSD) 98%, 99%. ^1H NMR (DMSO-d_6): 0.91 (t, 3H), 1.60 (m, 2H), 2.47 (t, 2H), 3.98 (s, 3H, OMe), 7.79 (s, 1H), 7.88 (dd, 1H), 8.39 (d, 1H), 9.50 (s, 1H, NH).

The following compound was prepared analagously using the appropriate acid chloride:

N-(2-Methoxy-4-nitrophenyl)-3,4-dichlorobenzamide.

LC/MS (m/z) 313.0 ($[M+H-NO]^+$, RT = 3.72, (UV, ELSD) 99%, 100%. ^{1}H NMR (DMSO-d_6): 4.00 (s, 3H, OMe), 7.82 (d, 1H), 7.88 (d, 1H), 7.93 (m, 2H), 8.17 (d, 1H), 8.20 (s, 1H), 10.01 (s, 1H, NH).

(2-(Furan-2-yl)-4-nitrophenyl)-carbamic acid propyl ester.

The mixture of (2-iodo-4-nitrophenyl)-carbamic acid propyl ester (30 mg, 0.086 mmol), 0.9 M aqueous K_2CO_3 (0.285 ml, 0.257 mmol), palladium (II) acetate (5 mg) and 2-furanboronic acid (48 mg, 0.428 mmol) in acetone (2 ml) was heated to +125°C for 3 min in the sealed vial under microwave irradiation. The obtained reaction mixture was evaporated and the title compound was purified by flash chromatography on SiO_2 (5 g, gradient heptane – ethyl acetate). Yield 21 mg, 84%. ^{1}H NMR ($CDCl_3$): 1.00 (t, 3H), 1.75 (m, 2H), 4.18 (t, 2H), 6.62 (dd, 1H, furan), 6.79 (d, 1H, furan), 7.64 (d, 1H, furan), 8.16 (dd, 1H), 8.36 (br. s, 1H, NH), 8.39 (d, 1H), 8.48 (d, 1H). LC/MS (m/z) 261.0 ($[M+H]^+$); RT = 1.57.

The following compound was prepared analogously with the appropriated boronic acid:

(2-Phenyl-4-nitrophenyl)-carbamic acid propyl ester.

The compound was used in the next step without purification.

(2-Methoxy-4-nitrophenyl)-carbamic acid ethyl ester

2-Methoxy-4-nitrophenylamine (5.0 g) was dissolved in dry dioxane (30 mL) and *N,N*-diisopropylethylamine (7.8 mL) was added at 0 °C. Ethyl chloroformate (4.25 mL) in dioxane (35 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature and stirred over night. Water (200 mL) was added and the mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic phase was washed with water (2 x 200 mL) and brine (200 mL), dried over sodium sulphate, filtered, and evaporated *in vacuo*. The crude product was recrystallised from ethanol to yield the title compound as colourless solid (4.45 g, 62 %).
^{1}H NMR (DMSO-d_6): 1.26 (t, 3H); 3.94 (s, 3H); 4.18 (q, 2H); 7.78 (d, 1H); 7.90 (dd, 1H); 8.09 (d, 1H); 8.99 (s, 1H).

(2-Hydroxy-4-nitrophenyl)-carbamic acid ethyl ester

(2-Methoxy-4-nitrophenyl)-carbamic acid ethyl ester (2.15 g) was dispensed in 1,2-dichloroethane (20 mL) and cooled to 0 °C. Boron tribromide (2.0 mL) in 1,2-dichloroethane (10 mL) was added dropwise. The reaction mixture was stirred 10 minutes at 0 °C and 30 minutes at room temperature. The mixture was again cooled to 0 °C, and water (10 mL) was added carefully. The reaction mixture was neutralised with saturated aqueous sodium bicarbonate and aqueous hydrochloric acid (5M). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over magnesium sulphate, filtered, and evaporated *in vacuo* to yield the title compound as brownish solid (1.96 g, 97 %).

^{1}H NMR (DMSO-d_6): 1.25 (t, 3H); 4.17 (q, 2H); 7.64 (d, 1H); 7.74 (dd, 1H); 8.01 (d, 1H); 8.69 (s, 1H); 10.96 (br s, 1H).

(2-Cyclopentyloxy-4-nitrophenyl)-carbamic acid ethyl ester

Cyclopentanol (7.24 mL, 376 mM in dry tetrahydrofuran) was added to triphenylphosphine (1.44 g, polystyrene bound, 1.89 mMol / g) under argon, followed by the addition of a solution of (2-Hydroxy-4-nitrophenyl)-carbamic acid ethyl ester (25.6 mL, 62 mM in dry tetrahydrofuran) and a solution of diethylazodicarboxylate (7.24 mL, 376 mM in dry tetrahydrofuran). The reaction mixture was shaken at room temperature over night. The resin was filtered and washed with THF (35 mL) and methanol (35 mL). The combined organic phase was evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel, heptane / ethyl acetate, gradient) to yield the title compound as slightly yellow solid (294 mg, 64 %).

^{1}H NMR (DMSO-d_6): 1.27 (t, 3H); 1.59 (m, 2H); 1.76 (m, 2H); 1.87 (m, 2H); 1.94 (m, 2H); 4.19 (q, 2H); 5.01 (h, 1H); 7.72 (d, 1H); 7.86 (dd, 1H); 8.11 (d, 1H); 8.82 (s, 1H).

The following compounds were prepared in an analogous fashion:

(4-Nitro-2-phenethyloxyphenyl)-carbamic acid ethyl ester

^{1}H NMR (DMSO-d_6): 1.28 (t, 3H); 3.15 (t, 2H); 4.19 (q, 2H); 4.38 (t, 2H); 7.23 (t, 1H); 7.32 (t, 2H); 7.36 (d, 2H); 7.80 (d, 1H); 7.88 (dd, 1H); 8.08 (d, 1H); 8.66 (s, 1H).

(2-Benzyloxy-4-nitrophenyl)-carbamic acid ethyl ester

^{1}H NMR (DMSO-d_6): 1.26 (t, 3H); 4.18 (q, 2H); 5.33 (s, 2H); 7.35 (t, 1H); 7.41 (t, 2H); 7.55 (d, 2H); 7.86 (d, 1H); 7.89 (dd, 1H); 8.06 (d, 1H); 8.95 (s, 1H).

(2-Isopropyloxy-4-nitrophenyl)-carbamic acid ethyl ester

^{1}H NMR (DMSO-d_6): 1.27 (t, 3H); 1.33 (d, 6H); 4.19 (q, 2H); 4.84 (h, 1H); 7.78 (d, 1H); 7.86 (dd, 1H); 8.12 (d, 1H); 8.77 (s, 1H).

Preparation of intermediates of the general formula XII

(4-Amino-2-methyloxyphenyl)-carbamic acid ethyl ester

(2-Methoxy-4-nitrophenyl)-carbamic acid ethyl ester (2.20 g) was dissolved in ethanol (220 mL). Aqueous hydrochloric acid (26 mL, 6 M) and iron powder (4.74 g) were added, and the mixture was stirred at 65 °C for 15 minutes. After cooling to room temperature, the mixture was neutralised with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 200 mL). The organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over magnesium sulphate, filtered, and evaporated in vacuo. The crude product was dissolved in ethanol (100 mL), and the above procedure was repeated using aqueous hydrochloric acid (26 mL, 6 M) and iron powder (3.7 g), to yield the title compound as a dark oil (1.80 g, 93 %). ^{1}H NMR (DMSO-d_6): 1.19 (t, 3H); 3.67 (s, 3H); 4.01 (q, 2H); 4.97 (s, 2H); 6.08 (dd, 1H); 6.23 (d, 1H); 6.97 (br s, 1H); 7.92 (br s, 1H).

(4-Amino-2-chlorophenyl)-carbamic acid ethyl ester.

To a cold (ice/water bath) vigorously stirred solution of crude (2-Chloro-4-nitrophenyl)-carbamic acid ethyl ester (5.8 g, 21.8 mmol) in THF (100 ml) and acetic acid (12 ml) zinc powder (20 g) was added by small portions maintaining the temperature below 40°C. The mixture was allowed to warm slowly to room temperatue and after reaction completion (1 hour) it was filtered via a plug of SiO_2 (20 g) with ethyl acetate as an eluent. The obtained solution was evaporated in vacuo and the crude yellow solid residue (4.9 g) was purified by precipitation from THF/Heptane to give 3.00 g of the title compound as pale yellow solid, yield 56%. LC/MS (m/z) 214, 216 (M^+); RT = 1.18, (UV, ELSD) 86%, 97%. ^{1}H NMR (DMSO-d_6): 1.18 (br. t, 3H); 4.02 (q, 2H), 5.29 (s, 2H, NH_2), 6.45 (dd, 1H), 6.61 (d, 1H), 6.98 (br. d, 1H), 8.52 (br. s, NHCO).

The following compounds were prepared analogously:

(4-Amino-2-chlorophenyl)-carbamic acid propyl ester.

Yield 84.6% (2.44 g, colorless solid). LC/MS (m/z) 228.1 (M^+); RT = 1.53, (UV, ELSD) 97.3%, 99%.

(4-Aminophenyl)-carbamic acid propyl ester.

Purified by flash chromatography on SiO_2 (gradient heptane – ethyl acetate). Dark purple crystalline solid, yield 3.066 g, 63.3%. LC/MS (m/z) 195 ($[M+H]^+$); RT = 1.18, (UV, ELSD) 87%, 98.3%.

(4-Aminophenyl)-carbamic acid ethyl ester.

LC/MS (m/z) 180.8 ($[M+H]^+$); RT = 0.48, (UV, ELSD) 71%, 97%.

(4-Amino-2-methoxyphenyl)-carbamic acid methyl ester.

LC/MS (m/z) 197.0 ($[M+H]^+$); RT = 0.49, (UV, ELSD) 71%, 98%.

(4-Amino-2-methoxyphenyl)-carbamic acid ethyl ester.

LC/MS (m/z) 210.9 ($[M+H]^+$); RT = 0.98, (UV, ELSD) 69%, 97%.

(4-Amino-2-methoxyphenyl)-carbamic acid isopropyl ester.

LC/MS (m/z) 224.0 (M^+); RT = 1.33, (UV, ELSD) 63%, 99%.

(4-Amino-2-methoxyphenyl)-carbamic acid propyl ester.

LC/MS (m/z) 224.9 ($[M+H]^+$); RT = 1.36, (UV, ELSD) 70%, 98%.

(4-Amino-2-methoxyphenyl)-carbamic acid 4-fluorophenyl ester.

LC/MS (m/z) 277.0 ($[M+H]^+$); RT = 1.64, (UV, ELSD) 44%, 93%.

(4-Amino-2-methylphenyl)-carbamic acid propyl ester.

LC/MS (m/z) 208.1 (M^+); RT = 1.16, (UV, ELSD) 95%, 100%. ^1H NMR ($CDCl_3$): 0.96 (t, 3H), 1.68 (m, 2H), 2.17 (s, 3H, Me), 3.59 (br. s, 2H, NH_2), 4.09 (t, 2H), 6.14 (br. s, 1H, ArH), 6.51 (m, 2H), 7.32 (br. s, 1H, NH).

(4-Amino-2-methylphenyl)-carbamic acid ethyl ester.

^{1}H NMR ($CDCl_3$): 1.28 (t, 3H), 2.16 (s, 3H, Me), 3.62 (br. s, 2H, NH_2), 4.19 (q, 2H), 6.16 (br. s, 1H, ArH), 6.5 (m, 2H), 7.31 (br. s, 1H, NH). LC/MS (m/z) 195.1 ($[M+H]^+$); RT = 0.75, (UV, ELSD) 70%, 95%.

(4-Amino-2-trifluoromethylphenyl)-carbamic acid ethyl ester.

^{1}H NMR ($CDCl_3$): 1.30 (t, 3H), 3.77 (br. s, 2H, NH_2), 4.20 (q, 2H), 6.52 (br. s, 1H, ArH), 6.82 (dd, 1H), 6.87 (unres. d, 1H), 7.65 (br. s, 1H, NH).). LC/MS (m/z) 248.1 (M^+); RT = 1.65, (UV, ELSD) 94%, 90%.

(4-Amino-2-trifluoromethylphenyl)-carbamic acid propyl ester.

^{1}H NMR ($CDCl_3$): 0.96 (t, 3H), 1.69 (m, 2H), 3.76 (br. s, 2H, NH_2), 4.11 (t, 2H), 6.51 (br. s, 1H, ArH), 6.81 (dd, 1H), 6.87 (d, 1H), 7.61 (br. s, 1H, NH). LC/MS (m/z) 261.9 (M^+); RT = 2.06, (UV, ELSD) 92%, 98%.

(4-Amino-2-cyanophenyl)-carbamic acid ethyl ester.

^{1}H NMR (DMSO-d_6): 1.21 (t, 3H), 4.07 (q, 2H), 5.49 (br. s, 2H, NH_2), 6.81 (m, 2H, ArH), 7.04 (d, 1H), 9.09 (br. s, 1H, NH). LC/MS (m/z) 204.9 (M^+), RT 1.05, (UV, ELSD) 98%, 99%.

(4-Amino-2-cyanophenyl)-carbamic acid propyl ester.

^{1}H NMR ($CDCl_3$): 0.98 (t, 3H), 1.71 (m, 2H), 3.72 (br. s, 2H, NH_2), 4.13 (t, 2H), 6.81 (br. s, ArH), 6.82 (d, 1H), 6.89 (dd, 1H), 7.83 (br. s, 1H, NH). LC/MS (m/z) 220.1 ($[M+H]^+$), RT = 1.52, (UV, ELSD) 98%, 100%.

N-(4-Amino-2-methoxyphenyl)-butyramide.

LC/MS (m/z) 208.9 ($[M+H]^+$), RT = 0.77, (UV, ELSD) 81%, 95%. ^{1}H NMR (DMSO-d_6): 0.89 (t, 3H), 1.56 (m, 2H), 2.22 (t, 2H), 3.4 (very br. s, NH_2), 3.69 (s, 3H, OMe), 6.08 (dd, 1H), 6.25 (d, 1H), 7.27 (d, 1H), 8.62 (s, 1H, NH).

N-(4-Amino-2-methoxyphenyl)-3,4-dichlorobenzamide.

LC/MS (m/z) 311.2 (M^+), RT = 1.93, (UV, ELSD) 100%, 100%. ^{1}H NMR (DMSO-d_6): 3.70 (s, 3H, OMe), 5.12 (br. s, 2H, NH_2), 6.15 (dd, 1H), 6.30 (d, 1H), 7.09 (d, 1H), 7.77 (d, 1H), 7.91 (dd, 1H), 8.17 (d, 1H), 9.46 (s, 1H, NH).

[4-Amino-2-(furan-2-yl)-phenyl]-carbamic acid propyl ester.

^{1}H NMR ($CDCl_3$): 0.96 (t, 3H), 1.68 (m, 2H), 3.65 (br. s, 2H, NH_2), 4.10 (t, 2H), 6.50 (dd, 1H, furan), 6.58 (d, 1H, furan), 6.66 (dd, 1H), 6.91 (br. s (unresolved d), 1H), 7.26 (br. s, ArH), 7.52 (d, 1H), 7.72 (br. s, 1H, NH). LC/MS (m/z) 261.0 ($[M+H]^+$); RT = 1.57.

(2-Phenyl-4-aminophenyl)-carbamic acid propyl ester.

LC/MS (m/z) 271.1 ($[M+H]^+$), RT = 1.75, (UV, ELSD) 57%, 99%.

(4-Amino-2-bromophenyl)-carbamic acid propyl ester.

A suspension of iron powder (20 g, excess) and (2-Bromo-4-nitrophenyl)-carbamic acid propyl ester (2.183 g, 7.20 mmol) in ethanol (80 ml) and 6 M aqueous hydrochloric acid (20 ml) was sonicated at room temperature for 10 min. The mixture was slowly poured into saturated aqueous $NaHCO_3$ solution, filtered and extracted with ethyl acetate. The combined organic solution was washed 3 times with $NaHCO_3$, dried over Na_2SO_4 and evaporated in vacuo to give 1.67 g of the title compound as pale yellow oil which solidified. Yield 85%. LC/MS (m/z) 271.9, 273.8 (M^+); RT = 1.30, (UV, ELSD) 99%, 100%. ^{1}H NMR (DMSO-d_6): 0.90 (br. s (unresolved t), 3H), 1.59 (br. s (unresolved m), 2H), 3.94 (t, 2H), 5.31 (s, 2H, NH_2), 6.50 (dd, 1H), 6.80 (unresolved d, 1H), 6.96 (br. d, 1H), 8.51 (br. s, NHCO).

The following compound was prepared analogously:

(4-Amino-2-iodophenyl)-carbamic acid propyl ester.

^{1}H NMR ($CDCl_3$): 0.97 (t, 3H), 1.69 (m, 2H), 3.59 (br. s, 2H, NH_2), 4.11 (t, 2H), 6.53 (br. s, 1H, ArH), 6.66 (dd, 1H), 7.11 (d, 1H), 7.61 (br. s, 1H, NH). LC/MS (m/z) 320.7 ($[M+H]^+$); RT = 1.71, (UV, ELSD) 98%, 99%.

Synthesis of intermediates of the general formulas XIII – XXIII:

N-(4-Amino-2-chlorophenyl)-2,2,2-trifluoroacetamide.

To a suspension of 4-nitro-2-chloroaniline (17.2 g, 0.1 mol) in 1,2-dichloroethane (100 ml) trifluoroacetic anhydride (16 ml, 0.113 mol) was added. Obtained yellow

solution was evaporated in vacuo after 5 min. The obtained yellow solid of N-(4-nitro-2-chlorophenyl)-2,2,2-trifluoroacetamide was reduced with the Zn-powder in THF-acetic acid as described above. The obtained crude product was treated with 2 M hydrochloric acid (150 ml) and diethyl ether. The obtained white precipitate was filtered to give 14.7 g of the title product as hydrochloride salt. The aqueous solution was neutralized with aq. sat. $NaHCO_3$ and filtered to give 4.58 g of the pure title compound as a pale grey solid. ^{1}H NMR (DMSO-d_6): 5.54 (br. s, 2H, NH_2), 6.53 (dd, 1H), 6.70 (d, 1H), 7.02 (d, 1H), 10.79 (br. s, 1H, NHCO). LC/MS (m/z) 239.8 ($[M+H]^+$); RT = 1.67, (UV) 100%.

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2,2-trifluoroacetamide.

A solution of N-(4-Amino-2-chlorophenyl)-2,2,2-trifluoroacetamide (4.567 g, 19.14 mmol) and 5-chlorothiophene-2-carboxaldehyde (3.97 g, 27.1 mmol) in anhydrous ethanol (50 ml) was heated to reflux for 15 min and evaporated in vacuo at 70°C (0.1 mbar, 30 min). The obtained crude imine as a crystalline solid was dissolved in methanol followed by addition of $NaBH_3CN$ in methanol (50 ml) and acetic acid (9 ml) by portions. The obtained reaction mixture was stirred at room temperature for 60 min and evaporated in vacuo to small volume. The concentrated solution was quenched with water and filtered after 30 min to give 6.98 g (99% yield) of the title compound as a brown-yellow solid. ^{1}H NMR (DMSO-d_6): 4.43 (d, 2H), 6.63 (dd, 1H), 6.77 (d, 1H), 6.79 (t, 1H, NH), 6.94 (d, 1H), 6.97 (d, 1H), 7.10 (d, 1H), 10.85 (br. s, 1H, NHCO). LC/MS (m/z) 367.9 (M^+); RT = 3.36, (UV, ELSD) 99%, 100%.

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2,2,2-trifluoroacetamide.

To a mixture of N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2,2-trifluoroacetamide (3.28 g, 8.88 mmol), 37% aqueous formaldehyde (5 ml), and acetic acid (3 ml), $NaBH_3CN$ (1.1 g) in methanol (10 ml) was added dropwise with stirring during 30 min. The reaction mixture was allowed to stand at room temperature for 2 hours and poured into water. After the oil solidified, it was filtered, washed with water and dried in vacuo to give 3.26 g of pale yellow-brown solid. Yield 95%. ^{1}H NMR (DMSO-d_6): 2.97 (s, 3H, NMe), 4.72 (s, 2H), 6.82 (m, 1H), 6.91

(m, 2H), 6.97 (d, 1H), 7.21 (d, 1H), 10.92 (br. s, 1H, NHCO). LC/MS (m/z) 382.0 (M^+); RT = 3.66, (UV, ELSD) 85%, 98%.

(5-Chloro-thiophen-2-ylmethyl)-[3-chloro-4-(2,2,2-trifluoro-acetylamino)-phenyl]-carbamic acid tert-butyl ester.

A mixture of N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2,2-trifluoroacetamide (2.219 g, 6.01 mmol), di-tert-butyl dicarbonate (2 g), and acetonitrile (3 ml) was heated to +80°C until reaction completion (36 hours). During this time additional amount of di-tert-butyl dicarbonate was added (2 x 1.5 g). The obtained reaction mixture was evaporated in vacuo (80°C, 0.1 mbar) to give the crude title compound which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6): 1.44 (s, 9H), 4.94 (s, 2H), 6.81 (d, 1H), 6.93 (d, 1H), 7.25 (dd, 1H), 7.43 (d, 1H), 7.50 (d, 1H), 11.24 (br. s, 1H, NHCO). LC/MS (m/z) 366.9 ([M-Boc]$^+$); RT = 3.99, (UV, ELSD) 87%, 96%.

2-Chloro-N(4)-(5-chloro-thiophen-2-ylmethyl)-N(4)-methyl-benzene-1,4-diamine.

To a solution of N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2,2,2-trifluoroacetamide (3.118 g) in MeOH (50 ml) solution of K_2CO_3 (6.4 g) in water (25 ml) was added and the reaction mixture was stirred until reaction completion (24 hours) at room temperature. The obtained reaction mixture was extracted with ethyl acetate, washed with sat. aq. $NaHCO_3$ and evaporated to give 2.26 g of dark brown oil which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6): 2.71 (s, 3H, NMe), 4.47 (s, 2H), 4.71 (br. s, 2H, NH_2), 6.67-6.75 (m, 3H), 6.82 (d, 1H), 6.93 (d, 1H). LC/MS (m/z) 288.0 ([M+H]$^+$); RT = 2.07, (UV, ELSD) 85%, 98%.

The following compound was prepared analogously:

(4-Amino-3-chlorophenyl)-(5-chloro-thiophen-2-ylmethyl)-carbamic acid tert-butyl ester.

^{1}H NMR (DMSO-d_6): 1.39 (br. s, 9H, tert-Bu), 4.74 (s, 2H), 5.35 (br. s, 2H, NH_2), 6.67-6.74 (m, 2H), 6.77 (br. d, 1H), 6.90 (d, 1H), 6.97 (d, 1H). LC/MS (m/z) 271.9 ([M-Boc]$^+$); RT = 3.73, (UV, ELSD) 77%, 97%.

4-Fluoro-2-isopropoxy-1-nitrobenzene

5-Fluoro-2-nitrophenol (48 g) was dissolved in dry THF (300 mL). Triphenylphosphine (88 g) and 2-propanol (47 mL) were added, and the resulting mixture was cooled to 0 °C. Diisopropylazodicarboxylate (66 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred over night. The solvent was evaporated *in vacuo* and the resulting mixture was filtered through silica (heptane / ethyl acetate 1:1). The solvent was evaporated *in vacuo* and the resulting mixture was recrystallised from heptane / ethyl acetate (1:1). The organic phase was separated from the crystalline solid by filtration, the solvent was evaporated *in vacuo*, and the remaining product was purified by flash chromatography (silica gel, heptane / ethyl acetate 9:1), yielding the title compound as colourless oil (47.2 g, 78 %).

^{1}H NMR (DMSO-d_6): 1.30 (d, 6H); 4.85 (h, 1H); 6.93 (m, 1H); 7.34 (dd, 1H); 7.96 (dd, 1H).

(4-Fluorobenzyl)-(3-isopropoxy-4-nitrophenyl)-(methyl)-amine

4-Fluoro-2-isopropoxy-1-nitrobenzene (1.0 g) was dissolved in dry dimethylsulfoxide (25 mL). Potassium carbonate (1.4 g) and (4-fluorobenzyl)-(methyl)-amine (0.84 g) were added. The resulting mixture was heated to 90 °C over night. After cooling to room temperature, water (75 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 75 mL). The organic phase was dried over sodium sulphate, filtered, and evaporated *in vacuo* to yield the title compound as slightly yellow solid (1.6 g, 100 %).

LC-MS (m/z) 319.1 (MH^+); RT = 3.43 (UV, ELSD) 85 %, 96 %.

^{1}H NMR (DMSO-d_6): 1.21 (d, 6H); 3.18 (s, 3H); 4.71 (m, 1H); 4.73 (s, 2H); 6.26 (d, 1H); 6.41 (dd, 1H); 7.17 (m, 2H); 7.25 (m, 2H); 7.84 (d, 1H).

4-(4-Fluorobenzyl)-(methyl)-amino-2-isopropoxyaniline

(4-Fluorobenzyl)-(3-isopropoxy-4-nitrophenyl)-(methyl)-amine (1.60 g) was dissolved in methanol (50 mL). Ammonium formiate (1.91 g) and palladium (10 % on charcoal, 0.21 g) were added, and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was filtered and the solvent was evaporated *in vacuo*. The residue was dissolved in a small amount of methanol, and concentrated

aqueous sodium hydroxide (2 mL) was added. The resulting mixture was filtered through a column of silica gel (ethyl acetate as eluent). The resulting solution was evaporated *in vacuo* to yield crude title compound as a black oil (0.76 g), which was directly used in the next step.

LC-MS (m/z) 288.9 (MH^+); RT = 1.91 (UV, ELSD) 80 %, 72 %.

Compounds of the invention

Example 1

1a *{4-[(Benzofuran-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.*

A mixture of 0.1 M solution of (4-amino-2-methylphenyl)-carbamic acid propyl ester (0.35 ml, 0.035 mmol) and 0.1 M solution of benzofuran-2-carbaldehyde (0.35 ml) in THF was kept at 55°C for 60 min. Volatiles were removed in vacuo. To the obtained residue 0.2 M $NaBH_3CN$ (0.5 ml) in methanol and acetic acid (0.03 ml) were added. After sonication for 60 min the reaction mixture was evaporated in vacuo and the title compound was separated by preparative LC/MS to give 5.1 mg of colorless solid. Yield 43%. LC/MS (m/z) 339.2 ($[M+H]^+$); RT = 2.92, (UV, ELSD) 94%, 94%.

1b *{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester.*

LC/MS (m/z) 323.9 (M^+); RT = 2.67, (UV, ELSD) 94%, 100%.

1c *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester.*

LC/MS (m/z) 340.0 (M^+); RT = 2.87, (UV, ELSD) 91%, 100%.

1d *{2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester.*

LC/MS (m/z) 365.3 ($[M-H]^+$); RT = 2.89, (UV, ELSD) 97%, 99%.

1e *[4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid ethyl ester.*

LC/MS (m/z) 326.0 (M^+); RT = 2.50, (UV, ELSD) 84%, 98%.

1f *[4-(4-Fluoro-benzylamino)-2-methylphenyl]-carbamic acid propyl ester.*

LC/MS (m/z) 317.1 ($[M+H]^+$); RT = 2.32, (UV, ELSD) 82%, 96%.

1g *(4-{[4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-2-methylphenyl)-carbamic acid propyl ester.*

LC/MS (m/z) 493.0 ($[M+H]^+$); RT = 3.18, (UV, ELSD) 91%, 97%.

1h *{4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 317.1 ($[M-H]^+$); RT = 2.41, (UV, ELSD) 76%, 93%.

1i *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 382.0 (M^+); RT = 2.96, (UV, ELSD) 70%, 87%.

1j *{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 338.2 (M^+); RT = 2.92, (UV, ELSD) 85%, 84%.

1k *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 355.1 ($[M+H]^+$); RT = 3.08, (UV, ELSD) 93%, 97%.

1l *{2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 379.3 ($[M-H]^+$); RT = 3.08, (UV, ELSD) 91%, 95%.

1m *[4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid propyl ester.*

LC/MS (m/z) 341.2 ($[M+H]^+$); RT = 2.71, (UV, ELSD) 73%, 96%.

1o *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester.*

LC/MS (m/z) 389.0 ($[M+H]^+$); RT = 3.24, (UV, ELSD) 98%, 99%.

1p *{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester.*
LC/MS (m/z) 345.0 ($[M+H]^+$); RT = 3.21, (UV, ELSD) 99%, 100%.

1q *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester.*
LC/MS (m/z) 361.0 ($[M+H]^+$); RT = 3.28, (UV, ELSD) 95%, 100%.

1r *[2-Chloro-4-(4-isopropyl-benzylamino)-phenyl]-carbamic acid ethyl ester.*
LC/MS (m/z) 346.0 (M^+); RT = 3.48, (UV, ELSD) 95%, 100%.

1s *[2-Chloro-4-(4-fluoro-benzylamino)-phenyl]-carbamic acid propyl ester.*
LC/MS (m/z) 337.1 ($[M+H]^+$); RT = 3.20, (UV, ELSD) 97%, 99%.

1t *2-Chloro-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid propyl ester.*
LC/MS (m/z) 514.2 ($[M+H]^+$); RT = 3.52, (UV, ELSD) 94%, 99%.

1u *{4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester.*
LC/MS (m/z) 337.0 ($[M-1]^+$); RT = 3.27, (UV, ELSD) 94%, 100%.

1v *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester.*
LC/MS (m/z) 403.9 ($[M+H]^+$); RT = 3.45, (UV, ELSD) 99%, 99%.

1w *{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester.*
LC/MS (m/z) 356.9 ($[M-H]^+$); RT = 3.43, (UV, ELSD) 98%, 95%.

1x *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester.*
LC/MS (m/z) 372.9 ($[M-H]^+$); RT = 3.49, (UV, ELSD) 93%, 99%.

1y *{4-[(Benzofuran-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester.*
LC/MS (m/z) 357.1 ($[M-H]^+$); RT = 3.37, (UV, ELSD) 95%, 98%.

1z *{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid ethyl ester.*
LC/MS (m/z) 335.0 (M^+); RT = 2.91, (UV, ELSD) 99%, 100%.

1aa *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid methyl ester.*
LC/MS (m/z) 341.1 (M^+); RT = 2.62, (UV, ELSD) 96%, 100%.

1ab *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid isopropyl ester.*
LC/MS (m/z) 400.0 (M^+); RT = 2.93, (UV, ELSD) 96%, 100%.

Example 2

2a *{4-[(4-Fluoro-benzyl)-(methyl)amino]-2-methoxyphenyl}-carbamic acid propyl ester.*

A mixture of (4-Amino-2-methoxyphenyl)-carbamic acid propyl ester (0.3 ml, 0.1 M solution in THF) and 4-fluorobenzaldehyde (0.3 ml, 0.1 M solution in THF) was heated to 50°C for 60 min and evaporated in vacuo. To the obtained residue $NaBH_3CN$ (0.6 ml, 0.2 M solution in methanol) and acetic acid (0.03 ml) were added. The reaction mixture was kept at room temperature for 30 min, then formaldehyde (0.03 ml, 37% in water) and acetic acid (0.03 ml) were added. After 30 min the reaction mixture was evaporated in vacuo. The title compound was separated by preparative LC/MS to give 4.3 mg of colorless solid, yield 41%. ^1H NMR (1:4 DMSO-H_6/DMSO-D_6): 8.04 (br. s, NH), 7.25 (m, 2H), 7.13 (m, 3H), 6.36 (s, 1H), 6.24 (d, 1H), 4.53 (s, 2H, CH_2), 3.93 (t, 2H), 3.70 (s, 3H, OMe), 2.97 (s, NMe), 1.57 (m, 2H), 0.89 (t, 3H). LC/MS (m/z) 347.2 ($[M+H]^+$); RT = 2.32, (UV, ELSD) 96%, 100%.

The following compounds were prepared analogously from appropriate anilines and aldehydes:

2b *[4-(Benzo[b]thiophen-2-ylmethyl-(methyl)amino)-2-methoxy-phenyl]-carbamic acid propyl ester.*

^{1}H NMR (1:4 DMSO-H_6/DMSO-D_6): 8.07 (br. s, NH), 7.86 (d, 1H), 7.76 (d, 1H), 7.30 (m, 4H), 6.49 (s, 1H), 6.36 (d, 1H), 4.83 (s, 2H, CH_2), 3.94 (t, 2H), 3.75 (s, 3H, OMe), 2.98 (s, NMe), 1.58 (m, 2H), 0.89 (t, 3H).). LC/MS (m/z) 385.0 ($[M+H]^+$); RT = 3.25, (UV, ELSD) 99%, 100%.

2c *{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 367.9 (M^+); RT = 3.07, (UV, ELSD) 99%, 100%.

2d *{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 412.1 (M^+); RT = 3.12, (UV, ELSD) 99%, 100%.

2e *{2-Methoxy-4-[methyl-(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester.*

LC/MS (m/z) 348.0 (M^+); RT = 2.46, (UV, ELSD) 95%, 100%.

Example 3

3a *{4-[(4-Fluorobenzyl)-(methyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester*

4-(4-Fluorobenzyl)-(methyl)-amino-2-isopropoxyaniline (0.29 g) was dissolved in dry dioxane (3 mL). *N,N*-Diisopropylethylamine (0.27 mL) and ethyl chloroformate (0.15 mL) were added, and the reaction mixture was stirred at room temperature over night. Water (5 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over sodium sulphate and filtered. The solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography (silica gel, heptane / ethyl acetate 19:1, 1 % triethylamine, gradient). Evaporation of the solvent *in vacuo* furnished the title compound (0.20 g, 55 %) as a colourless oil. LC-MS (m/z) 361.3 (MH^+); RT = 2.58 (UV, ELSD) 90 %, 98 %.

Example 4

4a *[4-(3-Fluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*

A solution of 3-fluorobenzaldehyde in dry methanol (84 µL, 476 mM) was added to a solution of (4-Amino-2-methyloxyphenyl)-carbamic acid ethyl ester (84 µL, 0.476 M in dry methanol). The resulting mixture was heated to 40 °C for 30 minutes. The solvent was evaporated *in vacuo*, and the remaining material was dissolved in 1,2-dichloroethane (1 mL). Sodium triacetoxyborohydrate (20 mg) was added, and the resulting mixture was kept at room temperature for 2 hours, under 2 periods of sonication for 10 minutes, respectively. The reaction mixture was filtered through silica gel (500 mg), and the column was washed with 1,2-dichloroethane (3 mL). The solvent was evaporated *in vacuo* yielding the title compound (5.7 mg, 45 %).
LC-MS (m/z) 318.1 (M^+); RT = 2.33 (UV, ELSD) 93 %, 100 %.

The following compounds were prepared in an analogous fashion:

4b *[4-(4-Isopropylbenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*
LC-MS (m/z) 341.3 ($M\text{-}1^+$); RT = 2.51 (UV, ELSD) 86 %, 100 %.

4c *{2-Methoxy-4-[(3-methylthiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester*
LC-MS (m/z) 319.9 (M^+); RT = 2.10 (UV, ELSD) 79 %, 99 %.

4d *[4-(2,4-Difluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*
LC-MS (m/z) 337.2 (MH^+); RT = 2.44 (UV, ELSD) 93 %, 100 %.

Example 5

5a *[2-Cyclopentyloxy-4-(4-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester*
(2-Cyclopentyloxy-4-nitrophenyl)-carbamic acid ethyl (294 mg) was dissolved in ethanol (26 mL). Zinc granules (1.63 g) and aqueous hydrochloric acid (5.0 mL, 2 M) were added. The resulting mixture was sonicated at room temperature for 6.5 hours, and then kept standing at room temperature over night. Aqueous saturated sodium bicarbonate (100 mL) was added, and the mixture was extracted with ethyl acetate (2 x 100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over magnesium sulphate, and evaporated in vacuo. The resulting oil was dissolved in methanol (1.82 mL), and an aliquot (40 µL) of this solution was mixed

with a solution of 4-methoxybenzaldehyde (40 µL, 0.466 M in methanol). The resulting mixture was heated to 40 °C for 20 minutes. The solvent was evaporated in vacuo, and the remaining material was dissolved in 1,2-dichloroethane (1 mL). Sodium triacetoxyborohydrate (20 mg) was added, and the resulting mixture was kept at room temperature for 2 hours, under 2 periods of sonication for 10 minutes, respectively. The reaction mixture was filtered through silica gel (500 mg), and the column was washed with 1,2-dichloroethane (3 mL). The solvent was evaporated in vacuo yielding the title compound (6.0 mg, 84 % from aldehyde).
LC-MS (m/z) 384.1 (M^+); RT = 2.40 (UV, ELSD) 76 %, 96 %.

The following compounds were prepared in an analogous fashion:

5b *[2-Cyclopentyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester*
The product was purified by preparative LC-MS.
LC-MS (m/z) 386.2 (M^+); RT = 3.22 (UV, ELSD) 80 %, 91 %.

5c *[4-(3-Fluoro-2-methylbenzylamino)-2-phenethyloxyphenyl]-carbamic acid ethyl ester*
The product was purified by preparative LC-MS.
LC-MS (m/z) 422.3 (M^+); RT = 3.38 (UV, ELSD) 84 %, 91 %.

5d *[2-Benzyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester*
The product was purified by preparative LC-MS.
LC-MS (m/z) 409.2 (MH^+); RT = 3.30 (UV, ELSD) 80 %, 89 %.

5e *[2-Benzyloxy-4-(4-methylsulfanylbenzylamino)-phenyl]-carbamic acid ethyl ester*
LC-MS (m/z) 422.1 (M^+); RT = 2.92 (UV, ELSD) 83 %, 89 %.

5f *{4-[(Benzo[b]thiophen-3-ylmethyl)-amino]-2-cyclopentyloxyphenyl}-carbamic acid ethyl ester*
The product was purified by preparative LC-MS.

LC-MS (m/z) 411.1 (MH^+); RT = 3.12 (UV, ELSD) 79 %, 85 %.

5g *[4-(3-Fluoro-2-methylbenzylamino)-2-isopropoxyphenyl]-carbamic acid ethyl ester*

The product was purified by preparative LC-MS.

LC-MS (m/z) 361.2 (MH^+); RT = 2.95 (UV, ELSD) 77 %, 86 %.

5h *[2-Benzyloxy-4-(3-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester*

LC-MS (m/z) 407.3 (MH^+) RT = 2.81 (UV, ELSD) 76 %, 87 %.

5i *{4-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester*

LC-MS (m/z) 372.1 (M^+); RT = 2.24 (UV, ELSD) 76 %, 86 %.

In vitro and in vivo testing

The compounds of the invention have been tested and shown effect in one or more of the below models:

Relative efflux through the KCNQ2 channel.

This exemplifies a KCNQ2 screening protocol for evaluating compounds of the present invention. The assay measures the relative efflux through the KCNQ2 channel, and was carried out according to a method described by Tang et al. (Tang, W. et. al., *J. Biomol. Screen.* **2001**, 6, 325-331) for hERG potassium channels with the modifications described below.

An adequate number of CHO cells stably expressing voltage-gated KCNQ2 channels were plated at a density sufficient to yield a mono-confluent layer on the day of the experiment. Cells were loaded with 1 µCi/ml [^{86}Rb] over night. On the day of the experiment cells were washed with HBSS-containing buffer. Cells were pre-incubated with drug for 30 min. and the $^{86}Rb^+$ efflux was stimulated by 15 mM KCl in the continued presence of drug for additional 30 min. After the incubation period, the supernatant was removed and counted in a liquid scintillation counter (Tricarb). Cells were lysed with 2 mM NaOH and the amount of ^{86}Rb+ was counted. The relative

efflux was calculated $((CPM_{super}/CPM_{super}+ CPM_{cell})_{Cmpd}/ (CPM_{super}/CPM_{super}+ CPM_{cell})_{15mM\ KCl})*100-100$.

The compounds of the invention have an EC_{50} of less than 20000nM. Accordingly, the compounds of the invention are useful in the treatment of diseases associated with the KCNQ family potassium channels.

Electrophysiological patch-clamp recordings.

Voltage-activated KCNQ2 currents were recorded from mammalian CHO cells by use of conventional patch-clamp recordings techniques in the whole-cell patch-clamp configuration (Hamill OP et.al. *Pflügers Arch* **1981**; 391: 85-100). CHO cells with stable expression of voltage-activated KCNQ2 channels were grown under normal cell culture conditions in CO_2 incubators and used for electrophysiological recordings 1-7 days after plating. KCNQ2 potassium channels were activated by voltage steps up to + 80 mV in increments of 5-20 mV (or with a ramp protocol) from a membrane holding potential between – 100 mV and – 40 mV (Tatulian L et al. *J Neuroscience* **2001**; 21 (15): 5535-5545). The electrophysiological effects induced by the compounds were evaluated on various parameters of the voltage-activated KCNQ2 current. Especially effects on the activation threshold for the current and on the maximum induced current were studied.

Some of the compounds of the invention have been tested in this test. A left-ward shift of the activation threshold and/or an increase in the maximum induced potassium current is expected to decrease the activity in neuronal networks and thus make the compounds useful in diseases with increased neuronal activity - like epilepsia.

Maximum electroshock

The test was conducted in groups of male mice using corneal electrodes and administering a square wave current of 26mA for 0.4seconds in order to induce a convulsion characterised by a tonic hind limb extension (Wlaz et al. *Epilepsy Research* **1998**, 30, 219-229).

Pilocarpine induced seizures

Pilocarpine induced seizures are induced by intraperitoneal injection of pilocarpine 250mg/kg to groups of male mice and observing for seizure activity resulting in loss of posture within a period of 30 minutes (Starr et al. *Pharmacology Biochemistry and Behavior* **1993**, 45, 321-325)

Pentylenetetrazole threshold test

The threshold dose of pentylenetetrazole required to induce a clonic convulsion was measured by timed infusion of pentylenetetrazole (5mg/ml at 0.5 ml/min) into a lateral tail vein of groups of male mice (Nutt et al. *J Pharmacy and Pharmacology* **1986**, 38, 697-698).

Side effects

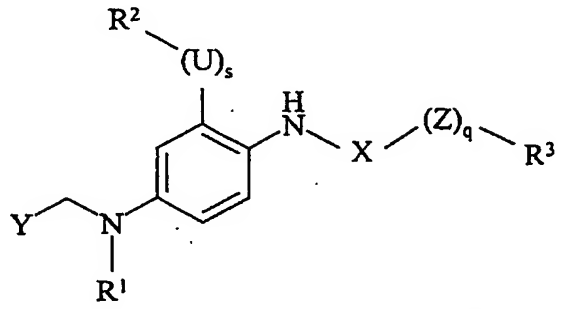
Central nervous system side-effects were measured by measuring the time mice would remain on rotarod apparatus (Capacio et al. *Drug and Chemical Toxicology* **1992**, 15, 177-201).

Pharmacokinetics

The pharmacokinetic properties of the compound were determined via. i.v. and p.o. dosing to Spraque Dawley rats, and, thereafter, drawing blood samples over 20 h. Plasma concentrations were determined with LC/MS/MS.

Claims

1 A substituted p-diaminobenzene derivatives of the general formula I



(I)

wherein

s is 0 or 1;

U is O, S, SO_2, SO_2NR^{11}, CO-O or CO-NR^{11}; wherein R^{11} is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or $\mathbf{R^2}$ and $\mathbf{R^{11}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

q is 0 or 1;

X is CO or SO_2; with the proviso that **q** is 0 when **X** is SO_2;

Z is O or S;

$\mathbf{R^1}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

R^2 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl and $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; wherein R^{10} and $R^{10'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or R^{10} and $R^{10'}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

provided that when R^2 is halogen or cyano then s is 0; and

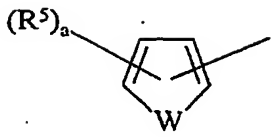
provided that U is O or S when s is 1 and R^2 is a hydrogen atom or acyl;

R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, heterocycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-

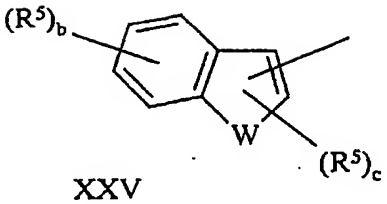
cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, $-NR^{12}R^{12'}$; wherein $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

and

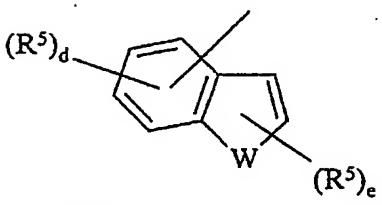
Y represents a group of formula XXIV, XXV, XXVI, XXVII or XXVIII:



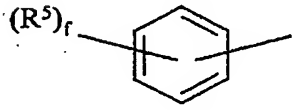
XXIV



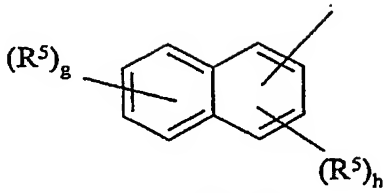
XXV



XXVI



XXVII



XXVIII

wherein

the line represents a bond attaching the group represented by Y to the carbon atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yloxy, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -$NR^7R^{7'}$, -S-R^8 and -SO_2R^8, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring which optionally contains one or two heteroatoms;

$\mathbf{R^6}$ and $\mathbf{R^{6'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

$\mathbf{R^7}$ and $\mathbf{R^{7'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

$\mathbf{R^8}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein $\mathbf{R^9}$ and $\mathbf{R^{9'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

or salts thereof.

2 A compound according to Claim 1, wherein $\mathbf{R^1}$ is selected from the group consisting of hydrogen and C_{1-6}-alk(en/yn)yl.

3 A compound according to any of Claims 1-2, wherein **s** is 0.

4 A compound according to any of Claims 1-2, wherein **s** is 1.

5 A compound according to Claim 4 wherein **U** is O.

6 A compound according to any of Claims 1-5, wherein $\mathbf{R^2}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl, halogen and cyano; provided that when $\mathbf{R^2}$ is halogen or cyano then **s** is 0.

7 A compound according to any of Claims 1-6, wherein **X** is CO.

8 A compound according to any of Claims 1-7, wherein **q** is 1.

9 A compound according to Claim 8, wherein Z is O.

10 A compound according to any of Claims 1-9, wherein $\mathbf{R^3}$ is C_{1-6}-alk(en/yn)yl.

11 A compound according to any of Claims 1-10, wherein each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, Ar, C_{1-6}-alk(en/yn)yloxy, halogen, -S-R^8 and -SO_2R^8, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring, which optionally contains one or two heteroatoms.

12 A compound according to Claim 11, wherein $\mathbf{R^8}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl and Ar .

13 A compound according to any of Claims 1-12, said compound being selected from the group consisting of:

1a {4-[(Benzofuran-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester
1b {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester
1c {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid ethyl ester.

1d {2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester.

1e [4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid ethyl ester

1f [4-(4-Fluoro-benzylamino)-2-methylphenyl]-carbamic acid propyl ester

1g (4-{[4-(4-Chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-2-methylphenyl)-carbamic acid propyl ester

1h {4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester

1i {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester.

1j {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester

1k {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methylphenyl}-carbamic acid propyl ester

1l {2-Methyl-4-[(5-phenyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

1m [4-(4-Isopropyl-benzylamino)-2-methylphenyl]-carbamic acid propyl ester

1o {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1p {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1q {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid ethyl ester

1r [2-Chloro-4-(4-isopropyl-benzylamino)-phenyl]-carbamic acid ethyl ester

1s [2-Chloro-4-(4-fluoro-benzylamino)-phenyl]-carbamic acid propyl ester

1t 2-Chloro-4-{[4-(4-chloro-benzenesulfonyl)-3-methyl-thiophen-2-ylmethyl]-amino}-phenyl)-carbamic acid propyl ester

1u {4-[(5-Methyl-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1v {4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1w{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

1x {4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1y {4-[(Benzofuran-2-ylmethyl)-amino]-2-chlorophenyl}-carbamic acid propyl ester

1z {4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid ethyl ester

1aa *{4-[(Benzo[b]thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid methyl ester*

1ab *{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-carbamic acid isopropyl ester*

2a *{4-[(4-Fluoro-benzyl)-(methyl)amino]-2-methoxyphenyl}-carbamic acid propyl ester*

2b *[4-(Benzo[b]thiophen-2-ylmethyl-(methyl)amino)-2-methoxy-phenyl]-carbamic acid propyl ester*

2c *{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester*

2d *{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-methoxy-phenyl}-carbamic acid propyl ester*

2e *{2-Methoxy-4-[methyl-(5-methyl-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester*

3a *{4-[(4-Fluorobenzyl)-(methyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester*

4a *[4-(3-Fluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*

4b *[4-(4-Isopropylbenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*

4c *{2-Methoxy-4-[(3-methylthiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid ethyl ester*

4d *[4-(2,4-Difluorobenzylamino)-2-methoxyphenyl]-carbamic acid ethyl ester*

5a *[2-Cyclopentyloxy-4-(4-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester*

5b *[2-Cyclopentyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester*

5c *[4-(3-Fluoro-2-methylbenzylamino)-2-phenethyloxyphenyl]-carbamic acid ethyl ester*

5d [2-Benzyloxy-4-(3-fluoro-2-methylbenzylamino)-phenyl]-carbamic acid ethyl ester

5e [2-Benzyloxy-4-(4-methylsulfanylbenzylamino)-phenyl]-carbamic acid ethyl ester

5f {4-[(Benzo[b]thiophen-3-ylmethyl)-amino]-2-cyclopentyloxyphenyl}-carbamic acid ethyl ester

5g [4-(3-Fluoro-2-methylbenzylamino)-2-isopropoxyphenyl]-carbamic acid ethyl ester

5h [2-Benzyloxy-4-(3-methoxybenzylamino)-phenyl]-carbamic acid ethyl ester

5i {4-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-2-isopropoxyphenyl}-carbamic acid ethyl ester.

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Cyano-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-carbamic acid propyl ester

{4-[(4-Isopropylbenzyl)-(methyl)amino]-2-methylphenyl}-carbamic acid propyl ester

{2-Methyl-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Methyl-4-[methyl-(4-methylsulfanyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid ethyl ester

{2-Chloro-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid ethyl ester

{2-Chloro-4-[methyl-(4-methylsulfanyl-benzyl)-amino]-phenyl}-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid propyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-chlorophenyl}-carbamic acid propyl ester

{2-Chloro-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(4-Isopropyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[Methyl-(4-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[Methyl-(4-methylsulfanyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-methyl-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(4-Isopropyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(4-tert!-Butyl-benzyl)-(methyl)amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[Methyl-(4-trifluoromethyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[Methyl-(4-methylsulfanyl-benzyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-(methyl)amino]-2-cyanophenyl}-carbamic acid propyl ester

{4-[(4-tert-Butyl-benzyl)-(methyl)amino]-2-cyanophenyl}-carbamic acid propyl ester

{2-Cyano-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-bromo-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(4-isopropylbenzyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(4-tert-butyl-benzyl)-(methyl)amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Iodo-4-(4-isopropyl-benzylamino)-phenyl]-carbamic acid propyl ester

[4-(4-tert-Butyl-benzylamino)-2-iodophenyl]-carbamic acid propyl ester

[2-Iodo-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Iodo-4-(4-methylsulfanyl-benzylamino)-phenyl]-carbamic acid propyl ester

{2-Iodo-4-[4-(4-methylpiperazin-1-yl)-benzylamino]-phenyl}-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid ethyl ester

[4-(4-tert-Butyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid ethyl ester

[4-(4-Methylsulfanyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid ethyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-trifluoromethyl-phenyl}-carbamic acid propyl ester

[4-(4-Isopropylbenzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[4-(4-tert-Butyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[2-Trifluoromethyl-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[4-(4-Dimethylamino-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

[4-(4-Methylsulfanyl-benzylamino)-2-trifluoromethyl-phenyl]-carbamic acid propyl ester

{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid propyl ester

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-cyanophenyl}-carbamic acid propyl ester

[2-Cyano-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

{2-Bromo-4-[(5-bromo-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

{2-Bromo-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-carbamic acid propyl ester

[2-Bromo-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-tert-butyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-trifluoromethyl-benzylamino)-phenyl]-carbamic acid propyl ester

[2-Bromo-4-(4-methylsulfanyl-benzylamino)-phenyl]-carbamic acid propyl ester

N-{4-[(5-Bromo-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-butyramide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-methoxyphenyl}-butyramide

N-[4-(4-Isopropylbenzylamino)-2-methoxyphenyl]-butyramide

N-[4-(4-tert-Butyl-benzylamino)-2-methoxyphenyl]-butyramide

N-[2-Methoxy-4-(4-trifluoromethyl-benzylamino)-phenyl]-butyramide

{4-[(5-Chloro-thiophen-2-ylmethyl)-amino]-2-furan-2-yl-phenyl}-carbamic acid propyl ester

[2-Furan-2-yl-4-(4-isopropylbenzylamino)-phenyl]-carbamic acid propyl ester

[5-(4-Fluorobenzylamino)-biphenyl-2-yl]-carbamic acid propyl ester

{5-[(5-Chloro-thiophen-2-ylmethyl)-amino]-biphenyl-2-yl}-carbamic acid propyl ester

[5-(4-Isopropylbenzylamino)-biphenyl-2-yl]-carbamic acid propyl ester

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-phenylacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3,3-dimethylbutyramide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-phenylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-butyramide

Pentanoic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclopropanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclobutanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclopentanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

Cyclohexanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-thiophen-2-yl-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(3-methoxy-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-chloro-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-methoxy-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2-(4-fluoro-phenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-cyclohexylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2-dimethylpropionamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-phenoxyacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-phenylacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-3,3-dimethylbutyramide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-butyramide

Pentanoic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclopropanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclobutanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclopentanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

Cyclohexanecarboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-thiophen-2-yl-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(3-methoxyphenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-chlorophenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-methoxyphenyl)-acetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2-(4-fluorophenyl)-acetamide

2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

2,3-Dihydro-benzofuran-5-carboxylic acid {2-chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-amide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-3-cyclohexylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-2,2-dimethylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-2-phenylacetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-3,3-dimethylbutyramide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-3-phenylpropionamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-butyramide

2,2,2-Trichloro-N-{4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-acetamide

Cyclopropanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methyl-phenyl}-amide

Cyclobutanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

Cyclopentanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

Cyclohexanecarboxylic acid {4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-amide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-thiophen-2-yl-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(3-methoxyphenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-malonamic acid methyl ester

2-(4-Chlorophenyl)-N-{4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(4-methoxyphenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-2-(4-fluorophenyl)-acetamide

N-{4-[(5-Chloro-thiophen-2-ylmethyl)-(methyl)amino]-2-methylphenyl}-3-cyclohexylpropionamide

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid phenyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid benzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid isobutyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid butyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid hexyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 4-nitrobenzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid but-3-enyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid but-2-ynyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2,2-dimethylpropyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2-chlorobenzyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 3-chloropropyl ester

{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-carbamic acid 2-benzyloxyethyl ester

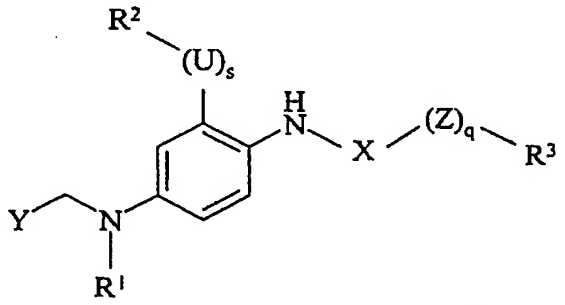
3-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-1-methyl-1-propyl-urea

1-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-3-(2-fluorophenyl)-urea

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-(methyl)amino]-phenyl}-2,2,2-trifluoroacetamide

N-{2-Chloro-4-[(5-chloro-thiophen-2-ylmethyl)-amino]-phenyl}-2,2,2-trifluoroacetamide

14 A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of the below formula I



(I)

wherein

s is 0 or 1;

U is O, S, SO_2, SO_2NR^{11}, CO-O or CO-NR^{11}; wherein R^{11} is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^2 and R^{11} together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

q is 0 or 1;

X is CO or SO_2; with the proviso that q is 0 when X is SO_2;

Z is O or S;

R^1 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

R^2 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl and $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; wherein R^{10} and $R^{10'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-

cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

provided that when $\mathbf{R^2}$ is halogen or cyano then **s** is 0; and

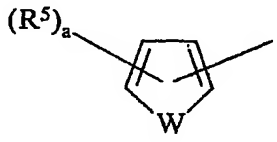
provided that **U** is O or S when **s** is 1 and $\mathbf{R^2}$ is a hydrogen atom or acyl;

$\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, heterocycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, $-NR^{12}R^{12'}$; wherein $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ are independently selected

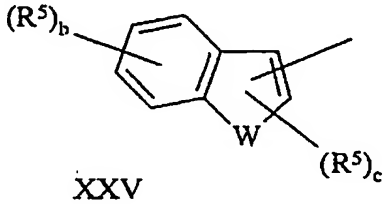
from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

and

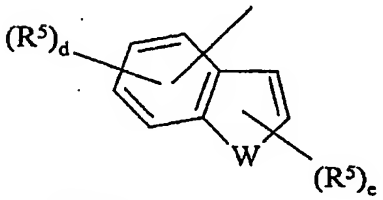
Y represents a group of formula XXIV, XXV, XXVI, XXVII or XXVIII:



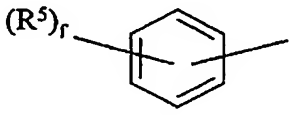
XXIV



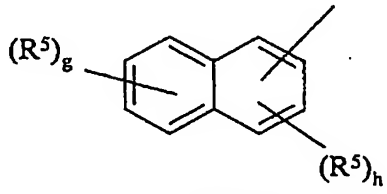
XXV



XXVI



XXVII



XXVIII

wherein

the line represents a bond attaching the group represented by Y to the carbon atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each $\mathbf{R^5}$ is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yloxy, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -$NR^7R^{7'}$, -S-R^8 and -SO_2R^8, or two adjacent $\mathbf{R^5}$ together with the aromatic group form a 5-8 membered ring which optionally contains one or two heteroatoms;

$\mathbf{R^6}$ and $\mathbf{R^{6'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

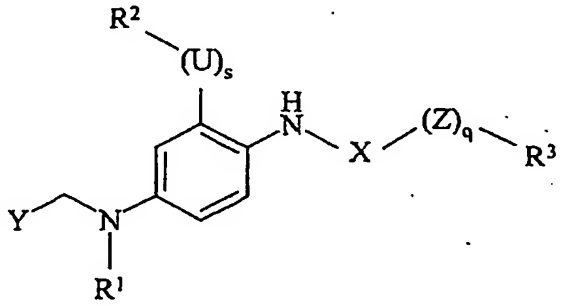
or salts thereof.

15 Use of a pharmaceutical composition according to Claim 14 for increasing ion flow in a potassium channel.

16 Use of a pharmaceutical composition according to Claim 15 for the prevention, treatment or inhibition of a disorder or condition being responsive to an increased ion flow in a potassium channel.

17 Use according to Claim 16, wherein said disorder or condition is selected from the group consisting of convulsions epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.

18 A method of increasing ion flow in a potassium channel, comprising administering a therapeutically effective amount of a compound of formula I



(I)

wherein

s is 0 or 1;

U is O, S, SO_2, SO_2NR^{11}, CO-O or CO-NR^{11}; wherein R^{11} is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or $\mathbf{R^2}$ and $\mathbf{R^{11}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

q is 0 or 1;

X is CO or SO_2; with the proviso that **q** is 0 when **X** is SO_2;

Z is O or S;

$\mathbf{R^1}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

$\mathbf{R^2}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{1-6}-alk(en/yn)yl, $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl and $NR^{10}R^{10'}$-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; wherein $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-

alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{10}}$ and $\mathbf{R^{10'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

provided that when $\mathbf{R^2}$ is halogen or cyano then s is 0; and

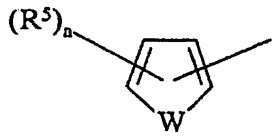
provided that **U** is O or S when s is 1 and $\mathbf{R^2}$ is a hydrogen atom or acyl;

$\mathbf{R^3}$ is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, heterocycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, Ar-heterocycloalk(en)yl, Ar-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, Ar-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{3-8}-cycloalk(en)yl, C_{1-6}-alk(en/yn)yloxy-heterocycloalk(en)yl, Ar-oxy-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy-carbonyl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-heterocycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-heterocycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-Ar, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-Ar, halo-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl-Ar, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-heterocycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, cyano-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl, acyl-C_{3-8}-cycloalk(en)yl, acyl-heterocycloalk(en)yl, acyl-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl-C_{1-6}-alk(en/yn)yl-C_{3-8}-cycloalk(en)yl, acyl-C_{1-6}-alk(en/yn)yl-heterocycloalk(en)yl, $-NR^{12}R^{12'}$; wherein $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-}

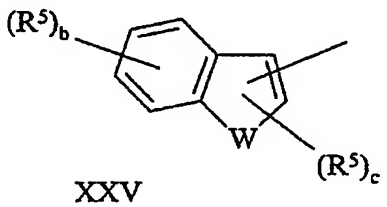
$_{8}$-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, hydroxy-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl and cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or $\mathbf{R^{12}}$ and $\mathbf{R^{12'}}$ together with the nitrogen atom form a 5-8 membered saturated or unsaturated ring which optionally contains 1, 2 or 3 further heteroatoms;

and

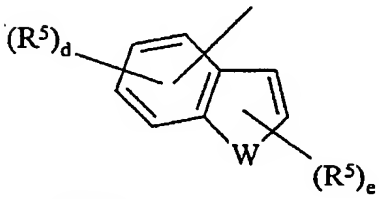
Y represents a group of formula XXIV, XXV, XXVI, XXVII or XXVIII:



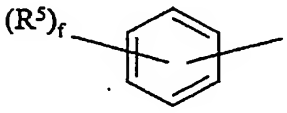
XXIV



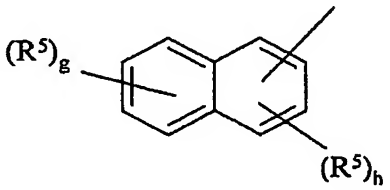
XXV



XXVI



XXVII



XXVIII

wherein

the line represents a bond attaching the group represented by Y to the carbon atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yloxy, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl, halo-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, cyano-C_{1-6}-alk(en/yn)yl, cyano-C_{3-8}-cycloalk(en)yl, cyano-C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, -$NR^7R^{7'}$, -S-R^8 and -SO_2R^8, or two adjacent R^5 together with the aromatic group form a 5-8 membered ring which optionally contains one or two heteroatoms;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;

or salts thereof.

19 Use of a pharmaceutical composition according to Claim 18 for increasing ion flow in a potassium channel.

20 A method according to Claim 19 for the prevention, treatment or inhibition of a disorder or condition responsive to an increased ion flow in potassium channel.

21 A method according to Claim 20, wherein said disorder or condition is selected from the group consisting of convulsions, epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.